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THE CELIAC SYNDROME

FACTORS INFLUENCING ITS DEVELOPMENT WITH PARTICULAR REFERENCE TO HYPOTHYROIDISM AS A CONTRIBUTING CAUSE

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THE term *celiac syndrome* has been suggested to describe a group of digestive disturbances characterized by intolerance to fat or starch, either or both, with no implication of a uniform etiology. The excretion of bulky, foul stools, and enlarged abdomen, malnutrition, retarded growth, and evidence of deficiency of one or more vitamins and minerals are part of the picture. The classification suggested by Andersen and Hodges[1] is as follows: (1) "celiac disease," in which the primary defect is in the absorption of fatty acids from the intestine; (2) cases in which there is dietary intolerance of starch but not of fat; (3) congenital pancreatic insufficiency; (4) chronic mechanical obstruction of the pathways of digestion and absorption; and (5) cases presenting or suggesting the celiac syndrome but which do not fall into the above groups.

In a more recent contribution, Andersen[2] states her feeling that the presence of steatorrhea is not required for the first group, since it was only transiently present in treated patients. Nine of her patients who showed it on first examination failed to show it on a normal diet including whole milk a few weeks later. Increasingly, there is a tendency to attribute a number of the findings in these chronic digestive disturbances to deficiency states resulting from faulty absorption and not basically a part of the fundamental disturbance.

No single etiologic factor has been found in the celiac syndrome which explains satisfactorily its pathogenesis, except in the group of pancreatic fibrosis cases. Nasopharyngeal infection is said to be the commonest finding in the experience of Holt and McIntosh,[3] and in twelve of our forty patients infection of the upper respiratory tract was prominent at the onset of the illness and during exacerbations. The frequency of this finding in children of the age group in which the syndrome is seen, and the rarity of the syndrome itself, call for a search for some other underlying conditioning factor which causes these children to react differently to such an infection than do otherwise normal children. A similar line of reasoning applies to the attributing of the symptoms to allergy;[4, 5] there are undoubted instances in which the failure of absorption

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seems referable to sensitivity, and yet a very small percentage of allergic individuals show the celiac syndrome. Five of our forty patients gave histories or findings suggesting allergy; though in none did it seem to be the entire explanation of the difficulty. None showed skin reactions to foods, though in two the introduction of an item found not to be tolerated would provoke abnormal stools. A third factor that we feel may well contribute to digestive difficulties, the psychogenic, is well accepted as a cause for a variety of gastrointestinal difficulties in older children and in adults, but seems not to have been considered seriously in this group. In the histories of eleven of our patients we were impressed by the possibilities of the role of insecurity, parental overanxiety, and frank mismanagement as contributing to the disturbance.

It has been our experience in a number of instances that the use of thyroid has been valuable in promoting a normal rate of growth when this has not been achieved by diet alone, and in some instances it has been valuable in shortening markedly the duration of the digestive symptoms also. Furthermore, there are a number of features in some cases of celiac disease which suggest hypothyroidism. It is the purpose of this paper to discuss thyroid deficiency as a factor contributing to the etiology of chronic intestinal indigestion.

A fourth factor always explored in the search for and explanation of a disturbance of growth is an endocrine one, and the following experiences are offered in support of the thesis that in a condition that may have multiple causes, thyroid deficiency is a conditioning factor in its development. Andersen's[2] recent hypothesis is that the condition is "believed to result from a deficiency of multiple nutritional factors complicating and resulting from a basic constitutional disease" and that "there is suggestive evidence that the difficulty in protein metabolism, shown by the high requirement for dietary protein and a tendency to hypoproteinemia on a normal diet, may be an expression of the basic disease." It is our thought that this "basic constitutional disease" may in some instances involve a thyroid deficiency on which is superimposed some other trigger mechanism such as infection, allergy, or emotion.

One of the outstanding findings in the condition is the disturbance of growth, and as we have watched the development of the condition in children whom we have followed from birth, we are impressed with the frequency with which a flattening of the curves of height and weight has preceded the abnormal stools. There has always been accepted as a part of the picture a retardation in the time of appearance of the centers of ossification, but this has been dismissed, somewhat gratuitously it seems to us, as a result of the fecal losses rather than as an integral part of the metabolic difficulty. In many of our cases it would appear that digestive symptoms have appeared later than would explain the retardation of bone age. Studies were done on thirty-two cases and showed delay in twenty-six, as judged by the standards of Vogt and Vickers[6] from the Harvard Growth Study. We were impressed with Todd's[7] statement that these have greater value when studied serially than

when attempt was made at a single assessment. Seventeen cases of pancreatic fibrosis are not considered here other than to point out that in seven of these in whom "bone age" was determined, in six it was found normal. If delay in the appearance of the centers of ossification were to be explained as a result of the digestive difficulty rather than an underlying cause, we should expect this group to show it in more extreme fashion than any. Osteoporosis was marked, but in only one was the appearance of centers delayed.

It seems to us significant that the commonest time of appearance of bowel symptoms, the latter half of the first year and the first half of the second (in twenty-three of our cases symptoms appeared between the seventh and eighteenth month of age), coincides with a decelerating phase and a falling rate of metabolism. It recalls a similar period in adolescence when the normal falling rate which follows the onset of puberty, physiologic though it be, carries with it a marked increase in the incidence of hypothyroidism. There is a normal tendency to recover from this fall; in Wetzel's[8] calculations an accelerating phase appears at 3½ years. Topper and Mulier[9] agree that the postpuberty fall likewise will be recovered from in the adolescent girl. The response of the anemia, the lassitude, the hypotension, low metabolism, and the menstrual irregularity to thyroid is so brilliant that to withhold this therapy would seem like poor judgment. Brailsford Robertson[10] in particular stressed the vulnerability of the decelerating phase of growth noted in the latter part of the first year. Again, the infrequency with which it is seen in the first few months suggests the situation seen in the cretin, whose failure to show the effects of his deficiency in the first few months results from the influences of his mother's hormone. However in seven cases there was a history of pylorospasm or enterospasm in the first few months.

Hypothyroidism and the celiac syndrome have in common abnormalities in the metabolism of protein, fat, carbohydrate, and calcium, and in gastrointestinal motility.

The effect of thyroid on protein is covered in two studies from this clinic.[11, 12] The high requirement for protein of which Andersen speaks is characteristic of the child with thyroid deficiency because this hormone is essential for the anabolic processes involving nitrogen in growth.

The flat oral tolerance curve noted in the celiac, admittedly nonspecific and common to a number of conditions, is seen in the hypothyroid.[13] Svensgaard[14] reports a series of studies with the oral tolerance curve on subjects that included cretins and celiacs. Both showed flat curves, those of the cretin becoming erect with thyroid. She did not give thyroid to celiacs. An average of the data on four of her cretins before and after treatment with thyroid is shown in Table I.

TABLE I. AVERAGE OF SVENSGAARD'S DATA ON FOUR CRETINS

	FASTING SUGAR	MAXIMAL VALUE	DURATION OF HYPERGLYCEMIA
Before	74	133	110 minutes
After	79	229	125 minutes

That the defect in the utilization of glucose in celiac disease involves a failure of absorption is generally conceded.[15] May and McCreary[16] concluded that their low blood sugar curves seem to be "merely a reflection of the inactivity in gastro-intestinal motility" and confirmed the findings of similar curves in the cretin. A similar failure is shown in the thyroidectomized animal in whom Althausen[17] shows a reduction in absorption of 50 per cent. This he attributes to a failure of the normal function of the thyroid in stimulating phosphorylation in the intestinal mucosa. Adequate replacement was shown to correct the deficiency rapidly and effectively.

Impaired fat absorption in the hypothyroid as measured by the vitamin A absorption test is of a degree comparable to that found in the celiac (Clausen and McCoord,[18] May and McCreary[19]), but whereas in the celiac carotene is also reported low, the hypothyroid is said to have an abnormally high level, his defect involving a failure of conversion of carotene to vitamin A. It could be expected, however, that when a condition characterized by poor absorption and steatorrhea is superimposed on one in which a hormone defect results in poor conversion, the carotene level would not be helpful. When it was found high, it was not at a time when diarrhea was prominent. Using the single dose four- or five-hour test,[20] ten of our cases showed a level of vitamin A of less than 30 μg, seven from 31 to 50 μg, and six higher than 50 μg. Carotene was below 100 μg in twelve, between 100 and 200 μg in four, and in seven it was over 200 μg. There were two abnormally high figures of 410 μg and 510 μg. The last figure was obtained on a subject who had had an adequate celiac diet but had not yet had thyroid.

In these studies a factor of 7.38 was used for the conversion of our values on carotene recorded in micrograms to the "units" of May and McCreary and 2.05 for converting micrograms of vitamin A to their units. Accordingly, the normal standards would be as shown in Table II.*

TABLE II

AGE GROUP	CAROTENE		VITAMIN A	
	MAY UNITS	μG	MAY 620 UNITS	μG
4 days-5 mo.	3.1- 7.5	22.0- 55	7.1-13	14-26.6
9 mo.-2 yr.	34.8-72.4	256.0-534	13.1-19.9	26-40
3 yr.-5 yr.	36.4-75	268.0-553	10.1-19.2	20-39
6 yr.-10 yr.	19.4-59	143.0-435	8.1-21.5	16-44
11 yr.-12 yr.	10.5-56	77.4-413	9.4-20.9	19-42

Rickets and tetany have both been seen in celiac disease and the failure to absorb calcium normally has been noted in balance observations.[21, 22] It was the negative calcium balance of the cretin made positive by thyroid that led us to use it in treating the obstinate tetany in the case of J. M. In a previous study,[23] we had shown that normal retentions of calcium could be expected only with a normal level of thyroid activity and that the cretin failed to store until he received thyroid, his losses being referable to large fecal excretions, the hyperthyroid's negative balances being the result of excessive losses both through the urine and the stool.

*For these calculations we are indebted to Dr. George H. Mangun.

Impairment of tone and sluggish peristalsis, held responsible for the clumping noted in celiac disease, are found in hypothyroidism, though Hamilton and associates[24] also demonstrated hypermotility of the stomach in adult hypothyroids becoming normal under treatment with thyroid.

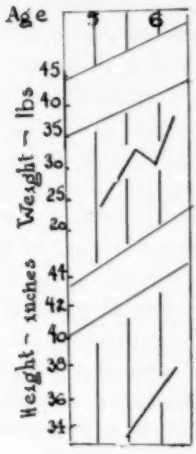
Thus a number of the findings seen in the one condition are duplicated in the other, save the abnormal stools. It is our thought that a certain percentage of infants have their digestive disorder precipitated by infection, emotion, and allergy, but that its development is conditioned by an underlying thyroid deficiency and that the complementing of the high protein diet with thyroid would notably shorten the duration of the mild case and in the severe case would correct an otherwise irreplaceable deficit.

The question will arise as to the confusion of a true primary hypothyroid state with the "hypometabolism" seen as a result, for example, of a low protein intake[25] or prolonged inactivity. In a study of two children[11] whose metabolic rate had fallen as a result of a year's inactivity, we showed that small amounts of thyroid were anabolic, as judged by the fact that they produced increased storage of nitrogen and calcium. Larger amounts became katabolic unless the intake were increased. It was possible to achieve an increased intake, however, only when the metabolic rate had been elevated with thyroid. The mechanism of the lowered rate of oxidation may be quite different in the two conditions, but there would seem to be the same usefulness in thyroid as a therapeutic agent, provided the dose is kept small.

The first experience leading to this thought was the demonstration of the effectiveness of thyroid in the correction of a failure to absorb calcium normally in two conventionally treated celiacs.

CASE 1.—T. M.,* a male child, was seen at 5 years of age with a history of onset of bowel disturbance at 1½ years. Abdominal enlargement and failure to gain had been noted for three years, and, although a high protein diet had been followed by a reduction in the number of stools from ten to two, the stools had continued to be large and frothy. The family history showed that one sibling has celiac disease and one a history suggestive of it. During the patient's first year his feeding history had not been unusual. He was breast-fed for three months, followed by lactic acid milk with Karo formula; cod liver oil was later replaced by 10 drops of viosterol; orange juice had been given since 3 months of age, cereal from 5 months, vegetables from 6, and eggs and meat after one year. Infection played no prominent role until the age of 3 years, when he had chicken pox, followed by pertussis at 4 and measles at 5 years. Stools showed a fat varying from 37 per cent to 63 per cent. Glucose tolerance (oral) was 55 mg., 50 mg., 61.5 mg., and 60 mg. at ½, 1, 2, and 3 hours. Intravenous pyelograms showed a double kidney pelvis, good excretion of the dye, and no dilatation of the pelves. Wrist plates showed a delay in ossification of at least two years. X-rays of the chest were negative. Blood calcium was 12.4 and phosphorus 3.0 mg. per cent. Blood showed 11.8 Gm. hemoglobin; white blood cells 3,800 with 64 per cent polymorphonuclears. Urine was negative. Barium meal showed the "clumping and segmentation noted in vitamin deficiency and celiac disease." Treated in another hospital from July, 1938, to August, 1938, he was discharged to a convalescent home until November, 1938, and to his home

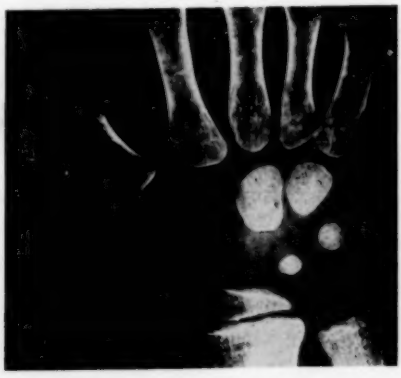
*For the case of T. M. we are indebted to Dr. James Wilson, Ann Arbor.



	Nitrogen		Calcium		Phosphorus	
	Control	Thyroid	Control	Thyroid	Control	Thyroid
Intake	11.46	11.55	1.550	1.568	1.640	1.656
Urine	7.71	8.33	0.040	0.031	0.599	0.721
Stool	1.39	1.46	1.530	1.411	0.726	0.715
Balance	2.36	1.76	-0.020	+0.126	0.353	0.280

A.

B.



C.

Fig. 1.—T. McP., 6 years of age. It had been possible to control the character of this boy's stools reasonably well with the celiac diet, but growth was unsatisfactory and he was subject to frequent relapses. Bone age was grossly delayed. *A*, Chart. *B*, X-ray at 5 years, 4 months of age. *C*, X-ray at 9 years, 4 months of age.

Note: In *A*, and the following charts the silhouettes were traced directly from the x-ray films. In all of these weight charts the "normal zone" represents the sixteenth and eighty-fourth percentiles of the Iowa standards.

after that. He was readmitted in March, 1939, with a history again of large, gray, foul stools. These improved in the hospital, though they remained quite large. Data on his growth are given in Table III.

TABLE III. DATA ON GROWTH OF T. M.

DATE	AGE	HEIGHT (INCHES)	WEIGHT (LB.)
July, 1938	5 yr., 4 mo.	33¾	23
November, 1938	5 yr., 8 mo.		32½
March, 1939	6 yr.	37	29
April, 1939	6 yr., 1 mo.	37	30
			Thyroid begun May 7, 1939
June, 1939	6 yr., 3 mo.	38	37

Balance studies for thirty-six days (significant figures for calcium require between fifteen and twenty days when the intake is not restricted) showed a negative balance for calcium entirely referable to fecal excretion, becoming positive with one grain of Burroughs-Wellcome thyroid for nine days and then two grains for eighteeen days, which resulted in a rise in basal calories from 763 to 887 per twenty-four hours. Interpretation of the "basal rate" is confused by the child's dwarfism; by the Boothby surface area standards these determinations would be minus 7 and plus 18, respectively.

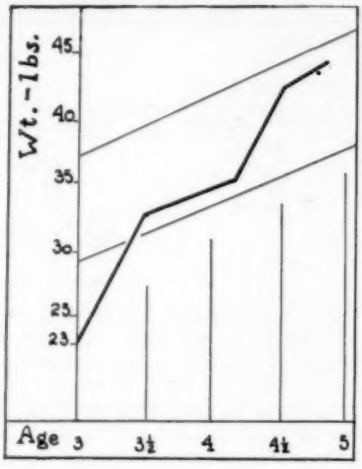
A negative calcium balance of 20 mg. per day was converted with thyroid to a positive balance of 126 mg. per day. Phosphorus and nitrogen retention fell slightly (Macy's[26] normal mean retention of calcium at 5 years was 172 mg. per day).

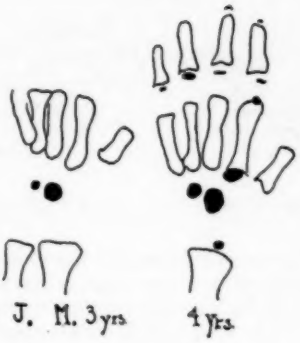
TABLE IV. T. M.

	NITROGEN (GM. PER DAY)		CALCIUM (GM. PER DAY)		PHOSPHORUS (GM. PER DAY)		BASAL CALORIES IN (24 HR.)		B.M.R. (BOOTHBY)	
	CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID	CONTROL	THYROID
Intake	11.46	11.55	1.550	1.568	1.640	1.656	763	887	−7	+18
Urine	7.71	8.33	0.040	0.031	0.559	0.721	--	--	--	--
Stool	1.39	1.46	1.530	1.411	0.726	0.715	--	--	--	--
Balance	2.36	1.76	−0.020	+0.126	0.355	0.280	--	--	--	--

CASE 2.—J. M.,* a male child born weighing 5 pounds apparently at term, did well nutritionally the first year on a diet of evaporated milk, water and Dextri-Maltose, orange juice, cod-liver oil, cereal, vegetables, and meat. History was uneventful until the age of 2½ years; he stood at 10 months but did not walk until 18 months of age. From 2½ to 3 years of age, he lost weight, the abdomen became distended, and the stools, at first yellow and watery, became large, foul, and frothy. Two months before admission the hands were noted to be held in spasm and there was some stiffening of the body. At this time, aged 3 years, he appeared severely malnourished, with little subcutaneous fat, shrunken buttocks, and a large abdomen. His measurements were as follows: length, 37 inches; weight, 23 pounds; head, 18¾ inches; and chest, 18 inches. He was showing definite tetany. The blood calcium was 7.3, phosphorus 2.1, phosphatase 0.8 units. The glucose tolerance curve was flat. He was treated for six weeks with calcium chloride, viosterol, and a celiac diet. He was referred to this clinic for balance studies, and at admission, aged 3 years, 3 months, the blood calcium was 5.0 mg. per cent, phosphorus 2.84 mg., and phosphatase 2.72 units. The wrist showed two

*For the case of J. M. we are indebted to Dr. Clement A. Smith, Boston.





	Control 18-day		Thyroid 16-day	
	Calcium	Nitrogen	Calcium	Nitrogen
Intake	353	15.60	836	14.36
Urine	87	8.52	47	7.36
Stool	812	1.48	496	1.53
Balance	54	5.60	293	5.47
%	5		35	

A.

B.

Fig. 2.—J. M.'s condition was complicated by recurrent tetany. Thyroid resulted in increasing his retention of calcium from 5 per cent of the intake to 35 per cent. *A*, Chart. *B*, X-ray at 3 years of age.

carpal centers at 3 years of age. Serum albumin was 3.18 and globulin 1.64. A balance study was conducted for thirty-six days, during the latter eighteen of which he received thyroid. The intake was derived from items in the celiac diet and was analyzed in duplicate for nitrogen and calcium.

TABLE V

	18-DAY CONTROL		THYROID ¼ GRAIN PER DAY. 18 DAYS	
	CALCIUM	NITROGEN	CALCIUM	NITROGEN
Intake	953 mg.	15.6 gm.	836 mg.	14.36 gm.
Urine	87	8.52	47	7.36
Stool	812	1.48	496	1.53
Balance	54	5.60	293	5.47

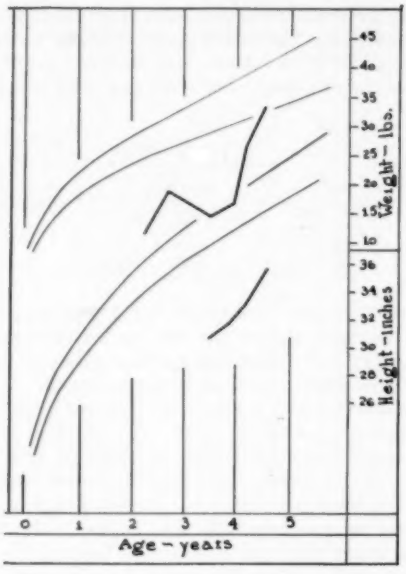
Seven months later he returned with the history of doing well until three months previous, when the stools became abnormal and he lost weight. At this time an intensive course of vitamin B parenterally was given following May's suggestion without measurable effect. Home cooperation on diet and medication was completely untrustworthy and he had several setbacks which the mother explained by the dropping of both thyroid and the diet and increasing of the starch intake. A 3-year-old plate showed marked osteoporosis and only two carpal centers. At 4 years the wrists showed only two centers on either side, with the radial head on one side. At 4½ years he had a recurrence of tetany. At this time his prothrombin was found to be 20 per cent of normal. At 5 and 5½ years there were recurrences of tetany, the blood on the last admission showing calcium of 7.4, phosphorus 6.3, and phosphatase of 3.2.

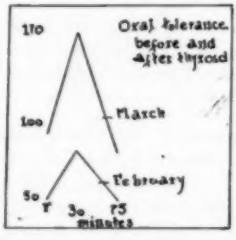
It could be concluded from this case that hypocalcemic tetany was correctable by replacement therapy with thyroid. Diet alone had been tried for three months. Thyroid was dropped for considerable periods before each of these readmissions.

CASE 3.—Ru. B., a female child, was seen at 6 years for dwarfism and failure to develop mentally; celiac stools were observed only intermittently. She was first studied in another institution at 2 years of age, unable to stand and weighing 13 lb. Stools were large but formed, save on occasions when they became loose and foul. She showed a marked retardation of bone age, a flat oral glucose tolerance curve, normal calcium and phosphorus, a phosphatase of 2 units, and cholesterol of 201. During the next two years she gained well while on a high protein, high vitamin diet but she entered the hospital four times, each time with a sharp loss of weight. At 4 years of age she weighed 15 lb. and was 30¾ inches in height. Her recovery after the diet was supplemented by thyroid was started as measured by height, weight, and bone development is recorded on the chart, but is not nearly so dramatic as her mental progress. The history of her twin, obtained from another institution, follows.

CASE 4.—Ro. B.,* a premature male twin of Ru. B., was hospitalized because of the complaint of slow mental development and dwarfism. He was 2 years old, weighed 11 pounds, 15 ounces, and was 26½ inches in height. The five other children were normal, as were the parents. He sat up at the age of 2 years. He did not appear ill, but was inactive. With a good diet the child gained one pound in seven days and seemed improved. During the following five months the child failed to improve at home, and was readmitted at the age of 2 years, 9 months, weighing 11 pounds, 9 ounces. He still did not talk, walk or stand alone. At this time bowel movements were stated to be large

*For the case of Ro. B. we are indebted to Dr. Paul V. Woolley, Detroit.





Basic phosphatase

2/47	2.87
12/47	1.68

A.

B.

C.

Fig. 3.—Ru. B. She was treated sporadically as a celiac for four years. No growth occurred until thyroid was started, although her stools could be controlled by a celiac diet. Her twin died with an identical history shortly before thyroid deficiency was appreciated in Ru. *A*, Chart. *B*, X-ray at 2 years, 9 months of age. *C*, X-ray at 7 years of age.

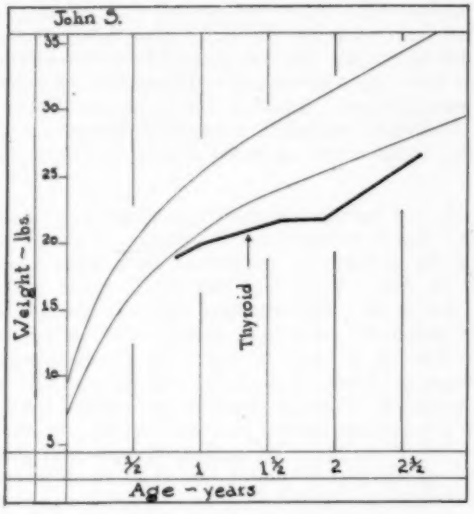
and foul. The x-rays of the long bones showed irregularity of the diaphyseal ends and patches of periostitis. The blood phosphorus was 5.5 mg. per cent, and phosphatase 0.9 Bodansky units. The blood cholesterol was 349 mg. per cent. The oral dextrose tolerance curve was 83, 90, 72, 75, and 67 mg. per 100 c.c. at fasting and 30, 60, 120, 180 minutes. He was placed in a convalescent home, and under careful feeding his weight increased to 24 pounds, 12 ounces, and he was sent home to convalesce further. Again under home care the child progressively failed and died. This child would, in retrospect, appear to have duplicated his sister's course and to have had as great a need for thyroid as she.

CASE 5.—R. K., a male child, was born at term of a mother said to have thyroid deficiency and arthritis. Birth weight was 8 pounds. Growth and development were fairly normal for a year; he walked at 13 months of age, and said several words at 17 months. From age one to 2 years he had grossly abnormal stools, six to ten a day, fermentative and greasy, and the abdomen became distended. He improved on a high protein diet. One hand became swollen at 2 years, one foot at 4 years of age. At about this time he appeared edematous, with frank puffiness of the eyes, and he was referred for study with a question of nephrosis, although studies in another hospital had shown a normal urine but a very low serum protein. At 4½ years the weight was 39 pounds, the height 39 inches. He appeared pale and puffy. There was frank swelling of the phalangeal joints of the right hand and the left ankle. Wrist studies showed only two carpal centers. Thyroid was begun and improvement was marked. The following observations were made eight months later: cholesterol 143; phosphatase 5.7 units: vitamin A absorption 13.8 μg per cent; carotene 54.2 μg per cent. Allergy tests showed reaction to alternaria, dust, and several bacterial proteins. Albumin was 2.05, globulin 1.46. Urine was negative. Cephalin cholesterol was negative. Stool fat was 19.3 per cent dry weight. An intercurrent respiratory infection in March, 1948, was followed by a recurrence of celiaclike stools and a loss of 3 pounds of weight.

TABLE VI

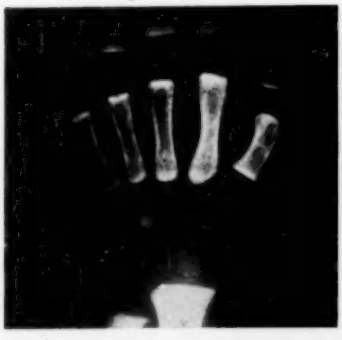
AGE	HEIGHT (INCHES)	WEIGHT (LB.)
Birth		8
4 yr., 4 mo.	39	39 (thyroid begun)
5 yr., 6 mo.	41	40

CASE 6.—The case of J. S. is offered as an example of the occurrence of the intestinal difficulty in a child in whom hypothyroidism had been suggested clinically four months before the stools became abnormal. Born normally and fed on an evaporated milk formula with added cereal and vegetables, his history was uneventful for fourteen months. A general check when he was 10 months of age occasioned the remark that he seemed an unusually placid baby and was not trying to pull himself erect. At that time he weighed 19 pounds, and the height was 28½ inches. At 14 months he returned with the complaint of five or six stools a day, marked irritability, and a flattening of the weight curve. The oral tolerance was 72, 76, 74, 54 mg. per 100 c.c. Vitamin A absorption was 31.0 μg and 180 μg carotene. Red blood count was 3,800,000; hemoglobin 10.9 Gm. Stool fat was 11 per cent dry weight. Wrist plate showed a single carpal bone at 16 months. Thyroid, grain ¼, was started, with a high protein diet; he was symptom-free in two months. On January, 1948, his height was 36 inches and weight, 27 pounds. The bone age in this case was sufficiently delayed to warrant the assumption that a re-



RBC 3.8 m. Hbg. 10.9 gm.
Glucose fol. - 72, 76, 74, 54 mg/100 cc
A absorption 31.9 mcg.
Carotene 180 mcg.

A.



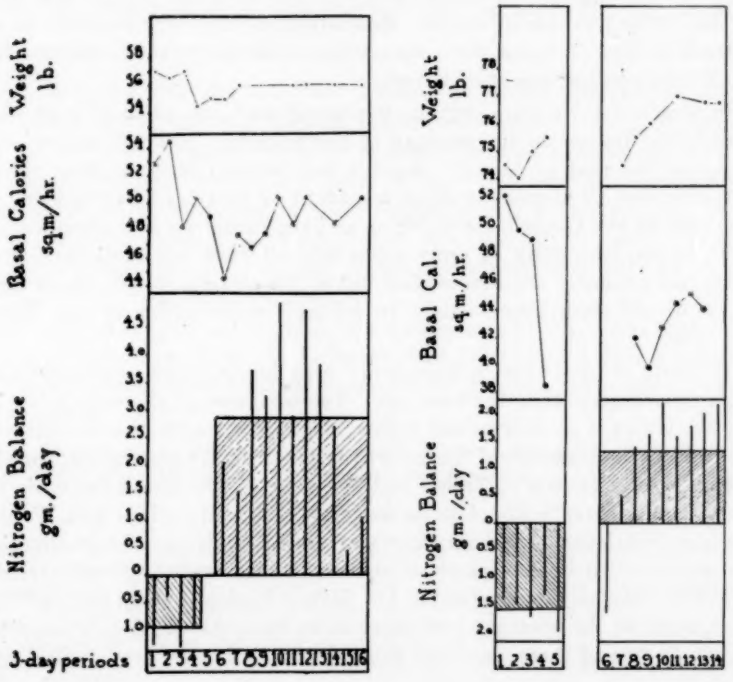
B.

C.

Fig. 4.—J. S.'s history suggested thyroid deficiency at 10 months of age; celiac symptoms appeared at 14 months of age. *A*, Chart. *B*, X-ray at 15 months of age. *C*, X-ray at 35 months of age.

tarding influence antedated the gastrointestinal symptoms. In addition, there were clinical signs of hypothyroidism, lethargy, and slowness in development at 10 months of age.

The role of infection of the lymphoid ring in activating the process might be understood again as an item fulfilling Andersen's[2] postulate. In a previous study,[27] from which we reproduce one chart, it was shown that tonsillar infection, even without fever, exerted a striking catabolic effect on protein metabolism and that the removal of infected tonsils and adenoids was followed promptly by an improved retention of nitrogen. These children, however, had elevated metabolic rates which fell after the operation. Infection was present in eighteen of the forty cases and in twelve it seemed to play a dominant role, but in ten of the eighteen cases we had no evidence of thyroid deficiency. In


Weight lb.
Basal Calories sq.m/hr.
Nitrogen Balance gm./day
3-day periods
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Weight lb.
Basal Cal. sq.m/hr.
Nitrogen Balance gm./day
1 2 3 4 5
6 7 8 9 10 11 12 13 14

A. *B.*

Fig. 5.—Chart showing the effect on the nitrogen balance of the removal of infected tonsils and adenoids. (From Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism, J. PEDIAT. 12: 563, 1938.

A, F. S., a boy 9 years old, height 50 inches, estimated weight, 58 pounds. Tonsillectomy was performed on the first day, fifth period. Nitrogen balance and basal metabolism were determined before and after removal of tonsils and adenoids. In this and subsequent charts the balances are continuous; each bar represents a three-day balance, and the average of all balances before and after is indicated by crosshatching.

B, S. R., a boy 13 years old, height 56 inches and estimated weight 78 pounds. Tonsillectomy was on the first day, sixth period. Nitrogen balance and basal metabolism were before and after removal of tonsils and adenoids. The balances, are continuous, and the diet constant. Each bar represents a three-day balance and the average of all periods before and after tonsillectomy is shown by crosshatching.

eight we felt we had. In twelve of the forty cases infection of the tonsils and adenoids, or the adenoids alone, seemed to have etiologic significance. In one (Case No. 12), our concern with it probably led to our overlooking the possibility of its being superimposed on a thyroid deficiency, and a bone plate was not taken until the age of 4½ years, when only two centers were found in the wrist and thyroid was started. Nevertheless, we feel that in some instances chronic infection of the adenoids and tonsils alone may constitute both the underlying metabolic flaw and the conditioning factor, and the usefulness of the procedure of tonsillectomy and adenoidectomy should be borne in mind constantly.

It would be well to stress again the fact that if thyroid is used, its anabolic effect will not be noted unless an increase in the intake of protein can be effected. In our original studies on the cretin, the increased storage was largely referable to an increase in intake. Recently in a juvenile myxedema no such increased storage occurred when we restricted the intake to the amount taken when the metabolism was at its lowest.

In this series we were further impressed with the probable role played by emotional factors in the etiology of the disturbed bowel function. Overanxiety on the part of parents, engendering fears in early infancy, the lack of affection and of normal handling attendant or prolonged institutional stays in the case of two illegitimate children, and the insecurity in several instances related to the instability of army camp life, all must have left their marks, and several instances are summarized out of the eleven cases in which we felt that emotional disturbances made an etiologic contribution to the digestive disturbance.

It would be desirable to have some more quantitative assessment of the hypometabolic state than the bone age. The weakness of cholesterol is widely accepted, unless it be determined before, during, and after the administration of thyroid. The response of the growth curve is highly suggestive. We have felt that the suggestion of Talbot and associates,[28] who found the basic phosphatase consistently below 4 units in the cretin, and of Hill and Webber,[29] whose low metabolism determinations and clinical evidences of hypothyroidism were accompanied by low phosphatase, was highly useful and we include in Table VII, through the courtesy of Dr. Sidney Farber, figures (in addition to those quoted in the protocols) on three cases from the Children's Hospital of Boston. In two of these cases the bone was one-half the chronological age.

TABLE VII

CALCIUM	PHOSPHORUS	PHOSPHATASE
7.8 mg.	4.7 mg.	3.5 units
7.7	6.4	3.6
7.0	4.4	2.3

However, in a controlled series of our own we have found, in a group of orphans from poor homes, phosphatase levels below 4 when there was no other evidence of hypothyroidism. We feel, however, that the demonstration

of improved calcium absorption in the two cases in whom balance determinations were reported, the acceleration of growth, and the shortening of the average time duration of symptoms, are all adequate reasons for considering that in a certain percentage of cases the hypometabolic state of the infant with celiac syndrome is improved with thyroid medication.

The addition of thyroid to the other items in the management of this condition has seemed notably to shorten the duration of symptoms, in eighteen cases the average being nine months, in contrast to seventeen in those treated with diet alone, and five children were symptom-free in less than two months. A number of patients whose thyroid therapy was not instituted until after several years of symptoms are not included. In a condition complicated by the development of deficiency states, it is not suggested that there be any departure from the practice of utilizing the high protein, high vitamin diet.

SUMMARY

In summary, we suggest that chronic intestinal indigestion may be precipitated by a number of factors, infectious, emotional, allergic, but, that since all of those suggested do not commonly produce the disorder in otherwise normal children, Andersen's[4] assumption of an underlying constitutional defect seems valid, and that in some instances this defect is a thyroid deficiency, while in others it is in the nature of a secondary hypothyroidism resulting from nitrogen and caloric deficits, in which cases thyroid in small doses is indicated for its anabolic effect.

We do not feel that thyroid deficiency explains all cases but that a number will be found in whom the defect will be referable to other mechanisms relating to protein synthesis. The role of the liver in these cases warrants further study.

Dr. Frank Hartman supervised the metabolism determinations.
Dr. Oliver H. Gaebler supervised the balance determinations.

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THE RELATION OF ILLNESS PATTERNS IN CHILDREN TO ORDINAL POSITION IN THE FAMILY

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THE long-term program of the Fels Research Institute includes seriatim medical examinations and interim health histories on approximately 300 children, who are being followed from prenatal life to maturity.[1] The present paper will be concerned with the illness records of 101 Fels children, forty-nine boys and fifty-two girls, during their first five postnatal years.

An attempt will be made to determine the extent to which a child's ordinal position in the family may be significantly associated with the type, incidence, and severity of certain disorders which he exhibits. The particular approach will be the study of various illness differentials as shown by singletons, first children, and second children.

Data on illness history are available from three sources:

1. A *medical examination,* given every third month during the first year, and every six months thereafter.

2. An *interval history,* a questionnaire mailed to all mothers at thirty-one intervals during the first five years: ten times during the first year, seven times during the second, six times during the third, and four times yearly thereafter. Information specifically requested includes details as to the duration and severity of illness, information on intestinal and urinary function, and problems of feeding. In the present study, 2,721 individual interval histories were evaluated.

3. An *illness history,* compiled by the Fels nurse, after conferences with the mother, during which the information sent in on the interval history is verified and complemented.

In the tabulation of illnesses, the following criteria were used:

Respiratory infections included colds, coughs, influenza, rhinitis, laryngitis, croup, pharyngitis, bronchitis, and pneumonia.

Tonsillitis was tabulated only when it was reported independently, not as a minor symptom accompanying a cold.

Vomiting included forcible expulsion, but not mild spitting up by infants under 9 months of age, nor vomiting with whooping cough.

Gastrointestinal disorders included such miscellaneous items as colic, nervous indigestion, bowel infection and intestinal influenza. If specific symptoms such as vomiting or diarrhea were reported, tabulation was made in those categories rather than here.

From The Fels Research Institute for the Study of Human Development, Antioch College.

Skin disorders included urticaria, eczema, miliaria rubra, impetigo, poison ivy, and boils.

Accidents included dog bites, burns, bruises, cuts, fractures, and concussions.

Feeding disorders: One "attack" was tabulated for each interval history which reported any anorexia or refusal to eat. Dislike or refusal of a few particular foods was not tabulated, nor was anorexia which occurred during an illness.

Mild: appetite reported as occasionally fair or fickle.

Severe: appetite reported as poor at recurrent intervals or frequently; any forced feeding.

Constipation was tabulated in the same manner as feeding problems. Constipation occurring during a cold or other illness was not tabulated, nor constipation lasting less than two days.

Mild: irregular movements and occasional laxatives.

Moderate: frequent irregularity, laxatives given once or twice weekly.

Severe: chronic; laxatives given almost daily.

Enuresis: Unlike the other illnesses studied, this was recorded only between 48 and 60 months of age. Both nocturnal and diurnal "accidents" were tabulated.

Other illnesses tabulated included asthma, whooping cough, ear infections, and diarrhea.

Degree of severity was estimated in nine of the illness categories as mild, moderate or severe . Criteria for feeding disorders and constipation have been described. Ratings on other illnesses were based on duration, degree of fever, and medical care required.

Of the thirty-one interval histories sent each family, the following average number of reports were returned and verified by the Fels nurse: singletons, 27.4; first children, 27.9; second children, 27.5. Many of the illnesses reported of course, were based on the diagnosis of the family physician. However, it is recognized that the mothers, who provided much of the raw material for this study, employed many terms in a lay sense, and with the commonly accepted understanding of their meaning. It is further realized that the data may reflect, in part, the parents' emotional attitudes in interpreting the child's somatic symptoms.

Two approaches have been made to an analysis of the data. The *group study* examines illness differentials in incidence and severity in eighty-nine children: twenty-two singletons, thirty-four first children, and thirty-three second children. A second approach to the problem was made by selecting twenty-nine pairs of siblings, who were first and second children in the same family. These children were matched by age and by sequence of interval histories available, and their histories compared. This section of the paper is referred to as the *sibling study.*

RESULTS

The Group Study.—Table I shows the mean incidence, as seen in singletons, first children, and second children, for each illness category. Each group of children shows a distinctive illness picture.

TABLE I. ILLNESS PATTERNS OF SINGLETONS, FIRST CHILDREN, AND SECOND CHILDREN DURING THE FIRST FIVE YEARS OF LIFE

ILLNESS CATEGORY	MEAN NUMBER OF ILLNESSES PER CHILD		
	SINGLETONS	FIRST CHILDREN	SECOND CHILDREN
Respiratory infections	12.91	12.56	16.54
Ear infections	1.23	.74	1.67
Tonsillitis	.14	.38	.39
Whooping cough	.23	.20	.33
Vomiting	2.41	2.68	3.03
Diarrhea	2.50	2.15	3.21
Gastrointestinal disorders	1.50	1.06	1.15
Skin disorders	3.95	3.06	2.82
Accidents	.68	.85	1.18
Feeding disorders	8.54	6.76	6.88
Constipation	5.54	5.00	3.36
Enuresis	.36	.26	1.03
Asthma	.59	.12	.18
Total mean	40.58	35.82	41.77
Total after excluding first four categories (See text)	26.07	21.94	22.84
Number of children in each group	22	34	33

Singletons have the highest mean incidence of miscellaneous gastrointestinal upsets, skin disorders, feeding disorders, constipation, and asthma. Second children have the highest mean incidence in respiratory infections, ear infections, tonsillitis, whooping cough, vomiting, diarrhea, accidents, and enuresis.

First children, on the other hand, do not show the highest mean incidence in any of the illness categories studied. In eight of the items they show the lowest mean incidence.

An analysis was made of the significance of differences between the three groups of children, for each illness category, and also between the singletons and the combined group of first and second children. Those differences which were significant at the 5 per cent level or better are shown in Table II.

TABLE II. DIFFERENCES IN INCIDENCE OF ILLNESS WHICH SHOW STATISTICAL SIGNIFICANCE AT THE 5 PER CENT LEVEL

ILLNESS CATEGORY	HIGHER GROUP	LOWER GROUP
Asthma	Singletons	Combined first and second
Skin disorders	Singletons	Combined first and second
Enuresis	Second Children	Singletons
Enuresis	Second Children	First Children
Diarrhea	Second Children	First Children
Respiratory infections	Second Children	Singletons
Respiratory infections	Second Children	First Children
Combined feeding disorders and constipation	Singletons	Second Children
Combined feeding disorders and constipation	Singletons	Combined first and second
Allergies (see text)	Singletons	Second Children
Allergies (see text)	Singletons	Combined first and second

It will be noted that if the illnesses are taken as a whole, the total mean incidence for second children (41.77) slightly exceeds the total mean for singletons (40.58), and both values are distinctly higher than the mean of 35.82 for first children. If, however, the first four categories of infectious diseases are omitted (respiratory and ear infections, tonsillitis, and whooping cough), the mean incidence for singletons becomes 26.07, for second children 22.84, and for first children 21.94.

From a further inspection of the data, a separate grouping of "allergies" was made, combining allergic skin diseases and asthma. Singletons show a mean incidence of 2.91 cases, first children 1.29, and second children 1.15. The differences between singletons and second children, and between singletons and the combined group of first and second children, are significant at the 5 per cent level.

TABLE III. SEVERITY OF ILLNESS

ILLNESS CATEGORY	PERCENTAGE OF CASES CLASSED AS EITHER MODERATE OR SEVERE		
	SINGLETONS	FIRST CHILDREN	SECOND CHILDREN
Respiratory infections	37	32	38
Ear infections	78	56	53
Vomiting	30	32	29
Diarrhea	42	27	37
Gastrointestinal upsets	27	28	29
Accidents	27	17	28
Feeding disorders	22	29	22
Constipation	37	38	30
Enuresis	50	33	53

In Table III, the three groups of children are compared on the basis of percentage of cases tabulated as either moderate or severe, for each of nine illness categories. For example, each singleton in Table I had an average of 12.91 respiratory infections during the first five years of life. As seen in Table III, 37 per cent of these cases were classed as either moderate or severe.

Little difference is shown between the three groups in severity of vomiting and gastrointestinal upsets. Singletons show greater severity in diarrhea and ear infections, and together with second children, are higher in severity of respiratory infections and accidents. First children show the greatest severity in feeding disorders, and together with singletons, are higher in severity of constipation. Second children are slightly higher than singletons in severity of enuresis, and considerably higher than first children. When severe or habitual enuresis is considered separately, rather than being combined with the moderate category, the distribution is: singletons, 25 per cent; first children, 33 per cent; second children, 47 per cent.

The Sibling Study.—In this section, twenty-nine pairs of siblings were selected, each pair consisting of a first and second child in a family. Forty-six of the fifty-eight children were taken from the group study, and twelve new cases were added. Sixteen pairs of children were like-sexed. In each pair of

siblings, the number and age-intervals of each interval history were matched. The method of comparison of illnesses was essentially the same as in the group study.

TABLE IV. COMPARISON OF ILLNESSES IN TWENTY-NINE PAIRS OF MATCHED SIBLINGS

ILLNESS CATEGORY	MEAN NUMBER OF ATTACKS BY WHICH SECOND CHILD EXCEEDED SIBLING
Respiratory infections	3.14
Ear infections	.72
Diarrhea	.48
Feeding disorders	.72
Enuresis	.79
Asthma	.03
Allergies	.03
Accidents	.52
ILLNESS CATEGORY	**MEAN NUMBER OF ATTACKS BY WHICH FIRST CHILD EXCEEDED SIBLING**
Whooping cough	.03
Vomiting	.41
Skin disorders	.35
Constipation	1.28
No difference: Tonsillitis, gastrointestinal upsets.	

Table IV shows the mean incidence of cases by which second children exceed first children in various illness categories, and the number of cases by which first children exceed second children. The results are similar to the group comparisons of the previous section, the only difference being a slightly higher mean incidence of second children in allergies, and a smaller incidence in attacks of vomiting.

In the comparison of severity tabulations, the siblings show much the same pattern as was shown for the groups in Table III.

Thus, the results from the comparison of matched siblings substantially confirm the results of comparisons based on unmatched group samples.

DISCUSSION

The differential distribution of illness categories by ordinal position, as shown in the present study, offers material for speculation. Taylor,[2] writing on the adjustment problems of the only child, has described a series of longitudinal case studies. Chronic digestive disorders, constipation, anorexia, and skin disorders are included in the illnesses from which singletons tend to suffer. On the other hand, children with siblings were found to be more prone to colds, influenza, measles, mumps, and broken bones. The present findings appear to confirm his results. Taylor suggests that the narrow social environment of singletons, during their critical, formative years, is the causal factor associated with the illness differentials found.

It also seems to be a reasonable hypothesis that illnesses such as asthma, allergies, anorexia, constipation, skin disorders, and gastrointestinal upsets, from which singletons suffer more often than first or second children, may in part be a reflection of a more intense emotional environment created by oversolicitous parents. It has been pointed out by Bakwin and Bakwin[3] that singletons, and

to a lesser degree first children, tend to have overprotective, overindulgent, and overanxious parents, and this may frequently be channeled into an abnormal concern over health.

Sontag,[4] discussing some of the psychosomatic aspects of childhood, states that during infancy and early childhood, physiologic processes are relatively unstable, and even mild stress situations may produce significant degrees of somatic dysfunction. A circular chain of interaction may become established, wherein the parent's anxiety over the child's nutrition, toilet training or illnesses is a source of considerable tension to the child.

A rich background of case histories has been presented by Kanner,[5] demonstrating the frequency with which parental overprotection may complicate such disorders as constipation, anorexia, and enuresis. Considerable evidence has also been offered [6, 7] in support of the theory that emotional disturbances may, by lowering the threshold of sensitivity, appreciably influence the character, frequency, and severity of allergic manifestations, such as asthma and some skin disorders.

Concerning the illness patterns of first children, it has been suggested that they may be expected to exceed other groupings of children in those illnesses readily influenced by psychic factors, because of the trauma experienced by the shifting, at the birth of a sibling, from an overprotected life to that of rivalry for parental affection and attention. There is little evidence in our study to substantiate this theory. The first children in our study suffer fewer illnesses than either singletons or second children. They are significantly high only in their incidence of constipation, and in the severity of constipation and feeding disorders. It is possible these two characteristics may be utilized by first children as hostility or attention-getting devices.

The second children in our study show a significantly higher incidence in infectious diseases. Our records also indicate that fewer measures were taken to protect them from such contagious diseases as whooping cough. In addition, the exposure to infection is unavoidably increased because of contact with a sibling.

The high incidence of vomiting and diarrhea in second children often occurred as a concomitant symptom of acute infections. Since anorexia and constipation were not recorded as incidental symptoms of infections, they may be taken to represent functional behavior disorders and are found predominately among the singletons and first children.

The high incidence of accidents among second children may perhaps be attributed to the lessened anxiety on the part of parents, and hence less protection, and to less time available for precautionary measures. It is also possible that competition with an older sibling, when a second child is still physically immature, may increase the latter's accidents, and that an older sibling may sometimes precipitate or inflict injuries on a second child.

Second children significantly exceed both only and first children in the incidence and severity of enuresis. This finding was a somewhat unexpected result.

It could be postulated that younger children, not having yet achieved control of bladder function, may utilize enuresis more often as a method of competing with an older sibling for parental attention. Enuresis may also appear more frequently among second children with an increase in sexual excitement and sex play in the presence of a sibling. It is also possible that enuresis appears more often among younger siblings because it represents an arrest of development rather than a regression. One predisposing environmental factor seems to be lack of adequate training, due to parental overindulgence and carelessness concerning regularity of habits. Enuresis is likely to be excused on the ground that the child is as yet too small to be educated.[5]

First children, on the other hand, may use constipation as their pattern of disability. It is interesting to speculate that constipation, as exhibited in the present study by singletons and first children, and enuresis, as shown by second children, may represent two opposing tendencies in personality development. Constipation may involve control, mastery, withholding, and a kind of masochism, whereas enuresis may reflect self-indulgence, rebellion against control, and giving.

SUMMARY

A comparison was made of the illness records, during the first five years, of twenty-two singletons, thirty-four first children, and thirty-three second children. A similar comparison was made of twenty-nine pairs of matched siblings, consisting of first and second children. Fourteen illness categories are described, and the records for each group, both in incidence and severity of illness, are shown.

Singletons show the highest means incidence in gastrointestinal upsets, skin disorders, feeding disorders, constipation, asthma, and allergies. Second children lead in respiratory and ear infections, tonsillitis, whooping cough, diarrhea, accidents, and enuresis. First children do not show the highest mean incidence in any of the illness categories examined. Those comparisons showing statistically significant differences are indicated.

There is a discussion of the possible significance of the findings, in terms of parental attitudes and interaction of children within the family, and certain hypotheses are suggested to account for the differential distribution of illness categories.

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SUSTAINED SUMMER HEAT AND FEVER IN INFANTS

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NEW YORK CITY was subjected to a most severe and sustained heat wave during a five-day period in August, 1948. The atmospheric temperatures ranged between 70° F. and 101° F., with a mean of 90° F. for three consecutive days (second, third, and fourth days) and was followed on the fifth day by a mean temperature of 86° F. At the same time the humidity was low. As the heat spell continued, more and more of the infants on the wards of the Children's Medical Service at Bellevue Hospital developed temperature elevations for which no cause could be found by careful clinical and laboratory examinations. Because of the difficulty in determining the role played by the weather, a study was made of the thermal responses of infants under 2 years of age during the heat wave. A number of interesting observations resulted.

REVIEW OF THE LITERATURE

The effect of intense heat upon the adult has been amply evaluated and discussed in the medical literature. The pediatric aspects of the problem however, have not been adequately investigated.

The earliest available reference is by Meyer[1] who, in 1911, noted several cases of heatstroke in infants during an extremely hot summer in Berlin. These amounted to 4.2 per cent of the total number of patients in the Foundling Home during the summer; several terminated fatally. Abt,[2] in 1919, mentioned that infants have an incompletely developed heat-regulating mechanism whose instability is so marked that ". . . if the room is warm, the temperature may rise to 100° F. or 102° F. or even higher," and that normal and previously healthy children may suffer from heatstroke. Talbot,[3] in 1925, stated that ". . . when infants are subjected to excessive heat, their body temperature becomes elevated, they become restless and perspire profusely, and very often the respirations become as high as 186 per minute." In 1926, Adair and Stewart[4] concluded that high external temperatures at least influence the incidence of fever among newborn infants, and in 1927, Tyson[5] reported a number of cases of fever in newborn babies which ". . . were probably due to the excessive external temperatures." Dodd and Wilkinson,[6] in 1927, observed elevated temperatures in a small group of relatively well infants during a week of extreme heat and very little air movement. On the fifth day of excessive heat, a peak of 104.5° F. was reached in one case. Upon removing the patients to a cooler room, their temperatures rapidly returned to normal.

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Van der Bagert and Moravec,[7] in 1937, concluded that the temperature-regulating mechanism of children is little less susceptible to environmental changes than is that of the monkey. They stated further that, though the ordinary environment has little effect upon the body temperature of the adult, it has a very definite effect upon the young, and, that the older the child, the more stable is the thermoregulatory center. In 1940, Jones[8] pointed out an apparent predilection for heatstroke to occur in infancy or beyond the age of 70 years. Åkerren,[9] in 1943, stated that for purely physical reasons, owing to its small size, and also because of its probably less well-developed cerebral regulatory apparatus, the infant and young child is relatively poikilothermic in comparison with the older child or adult. The most recent report is that of Talbot[10] who, in 1948, concluded that, although physiologic regulation of body heat usually becomes adequate in the first three months of life, it may fail to compensate for extremes of heat and cold for a prolonged period. Throughout childhood most physiologic processes are more easily upset than they are in the mature individual and heat regulation is no exception.

SOURCE MATERIAL

The meteorologic data were obtained from the New York City Weather Bureau.[11] No records were kept of the ward temperatures but one may assume that they were at least as high as those reported by the Weather Bureau. In addition, the hospital temperatures probably did not undergo the diurnal variations which were reported for the outdoors. Ferris, Blankenhorn, and Harder,[12] in commenting on studies made by them during a heat wave in Cincinnati in 1938, found that the indoor temperatures were consistently 3° F. higher than those recorded out-of-doors. The explanation offered is that within buildings there is sluggish air movement which prevents dissipation of heat, and that this, in conjunction with the high heat-retaining capacity of construction materials (steel, concrete, etc.), maintains a higher and more stable atmospheric temperature indoors than outdoors.

A total of eighty-eight patients was included in this study. Twenty-four were newborn babies under 10 days of age, and the remaining sixty-four ranged from 10 days to 2 years of age. All temperatures were taken routinely by rectum at 8:00 A.M. and at 4:00 P.M. In the case of the acutely ill patients, and at the height of the heat wave, temperatures were taken every four hours or oftener as indicated. In the various graphs no point was plotted unless it represented the average of the temperatures of at least 70 per cent of the patients in any given group; where the patients within a group numbered less than five, each point is the average of the temperatures of all within the group.

The temperature readings for several days immediately preceding and following the heat wave were included, values being taken from August 22 to September 4, inclusive, for a total of fourteen days. No patient was included who did not have a hospital stay of at least seven days during this two-

week period, but all patients who were admitted because of hyperpyrexia during the heat wave were included in the calculations.

The eighty-eight patients were classified according to diagnosis and divided into five major groups:

I. Newborn infants		24
II. Well boarders		21
III. Congenital or acquired cerebral damage		24
Hydrocephalus and spina bifida	11	
Mongolian idiocy	7	
Microcephalus	1	
Achondroplasia	1	
Porencephalus	1	
Craniosynostosis	1	
Nonspecific birth injury	1	
Residual cerebral damage from type 14 pneumococcal meningitis	1	
IV. Diarrhea		3
V. Miscellaneous diseases		16
Primary pulmonary tuberculosis	4	
Nontuberculous pulmonary disease	2	
Miliary tuberculosis	1	
Tuberculous meningitis	1	
Chronic eczema	1	
Spinal deformity	1	
Erythroblastosis fetalis	1	
Omphalitis	1	
Letterer-Siwe's disease	1	
Congenital torticollis	1	
Congenital cataracts	1	
Inguinal hernia	1	

GENERAL EFFECT OF THE HEAT

Although the first rise in atmospheric temperature occurred on August 25, there was no significant rise in the average body temperatures until approximately thirty-six hours later, on the afternoon of August 26, when several patients, including the well boarders, developed temperatures above 101.0° F., one patient with hydrocephalus reaching 104.0° F. The three patients with diarrhea differed from the rest in that they showed a marked rise in temperature on the very first day of excessive heat, with individual values ranging between 101.0° F. and 103.4° F. In addition, whereas there was little clinical change among the remaining eighty-five patients, those with diarrhea rapidly deteriorated, appearing dehydrated, cachectic, and restless. At the same time the volume and number of watery stools increased.

After the initial thirty-six-hour lag phase, the patients, with few exceptions, showed progressive temperature elevations. Accordingly, a number of antipyretic measures were instituted. These included supplemental water feedings every two hours, removal of all clothing with the exception of diapers, repeated hypodermoclyses of a 3 per cent glucose and 0.3 per cent sodium chloride solution, and blanket orders for 1 gr. of aspirin and cool water sponging of all patients whose temperatures reached 102.0° F. or above.

On the morning of the third day of the heat wave (August 27), the patients were restless, irritable, and were eating poorly, though they took their additional water avidly. None showed evidence of infection. One gram of sodium chloride was added to the twenty-four-hour formulas of all

patients in an attempt to prevent salt depletion from profuse sweating which was noted in a number of babies. Because all formulas are prepared twenty-four hours in advance at Bellevue Hospital, the patients did not receive the additional salt until the following day (August 28). For purposes of control, salt was withheld from six patients, but these were unwittingly selected from among those who seemed to be withstanding the heat best of all. Consequently, no conclusions could be drawn as to the advantages or disadvantages of adding salt. However, somewhat startling results were obtained in those with diarrhea which will be discussed subsequently.

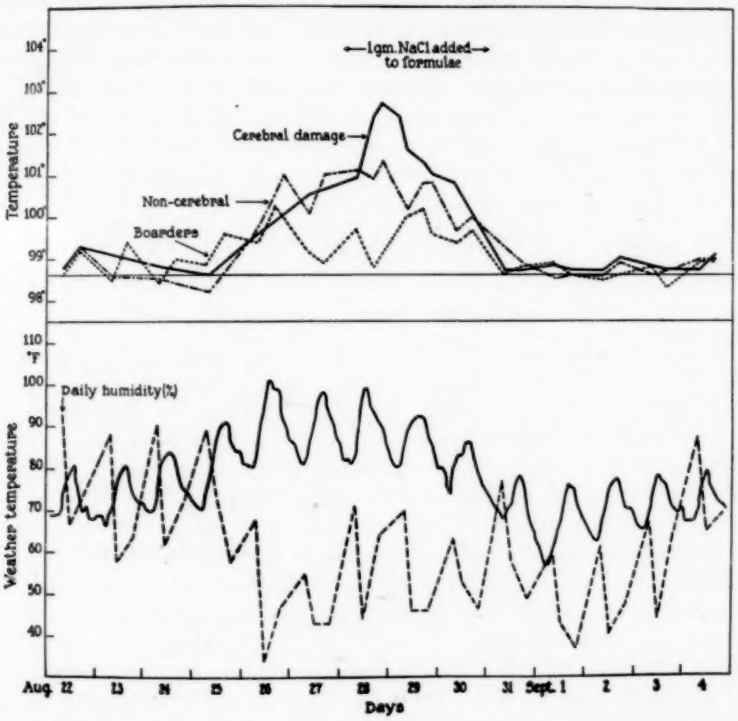

Fig. 1.—A comparison of the temperature responses of well infants, infants with miscellaneous noncerebral diseases, and infants with cerebral defects during the heat wave (Aug. 25 to 29, 1948).

The babies seemed to take their "salted" formulas better for the first two days, but on the third day, when the heat was abating, the older infants refused their feedings. The additional salt was continued through August 30, the first day of relatively normal environmental temperatures.

Despite all measures taken, the temperatures of the patients who had been ill previously, and those of the patients with various forms of cerebral disease, continued to rise until, on August 28, the fourth day of the heat wave, a peak average of 101.3° F. for those with previous illness (Group V) and

102.7° F. for those with cerebral damage (Group III) was reached. The temperatures for the well boarders (Group II), on the other hand, showed no further rise beyond the initial average elevation to 100.3° F. on the second day, although the individual variations ranged as high as 103.0° F. (Fig. 1).

Of the twenty-four patients with cerebral disease six died; of these, four had been in the hospital prior to the onset of the heat wave, and the remaining two were admitted during the period under consideration because of hyperpyrexia.

As the intense heat subsided toward the end of the fifth day, the average temperatures continued elevated for an additional twenty-four hours when normal levels were finally achieved. It is obvious, therefore, that all patients, with the exception of the three with diarrhea, seem to have been capable of adjusting to the abnormal environment during the initial period of the heat wave; when this capacity was lost, fever developed. Similarly, a "cooling off" period of about equal duration followed the recession of atmospheric heat before body temperatures returned to normal.

With the subsidence of the fevers, the irritability, the fretfulness, the poor appetites, and the marked thirsts passed.

EFFECT ON NEWBORN INFANTS

Whereas the temperatures of some fifty normal newborn infants during the ten days immediately preceding the heat wave did not exceed 100.0° F., of the twenty-four normal newborn infants in the nursery during the heat wave, six showed temperature elevations (one as high as 105.4° F.). This is consistent with the report of Adair and Stewart[4] who found that of 321 babies born during the summer months, 24.3 per cent developed fever. This led them to conclude that the high external temperatures of summer have a definite influence on the frequency of occurrence of fever in newborn infants.

The rise in body temperature in the six infants, which was associated with moderate to marked dehydration, promptly responded to the administration of adequate quantities of fluid. The temperature rises, usually of one day's duration and of a sudden, spiking nature, occurred between the second and fifth days of life. These were not associated with any unusual degree of restlessness or irritability. Salt was not added to their formulas. All infants made uneventful recoveries and were discharged within the usual period of time.

Several reports in the literature[13, 14] seem to be in accord that the heat-regulating capacity of the mature newborn infant, especially in the responses to excessive heat as contrasted with those toward cold, is fairly well developed, but that it is nevertheless influenced by sustained heat in the absence of adequate quantities of fluid.[4] Other authors[2, 3, 7, 9, 10] feel that the thermal regulatory center of the newborn infant is exceptionally labile, but that within a period of weeks or a few months its function, when exposed to extremes of heat and cold, becomes better stabilized.

It would appear that there is a greater degree of thermolability among older infants than in newborn babies inasmuch as a far larger proportion of the former developed fever. However, because of the small total number of patients no conclusions may be drawn.

EFFECT ON WELL BOARDERS

The boarders were a group of healthy and normally developed infants receiving custodial care on the wards of Bellevue Hospital while awaiting return to their homes or placement in foster homes. Of the total of twenty-one, eight were under 6 months of age, eight were between 6 months and 1 year, and five were between 1 and 2 years of age. There were ten girls and eleven boys. The racial distribution was ten white, five Puerto Rican, four Negro, and two yellow.

On August 25, with the first rise in weather temperature, four patients showed a rise above 100.0° F. but none reached 101.0° F.; the remaining seventeen showed no rise whatever. There was no change in their clinical behavior, and the highest average body temperature for this day was 99.6° F. This average temperature was maintained until the early evening of the next day, when it rose to 100.3° F. This was the highest average temperature registered by the boarders throughout the heat wave. On this day, of the twenty-one boarders, six had temperatures above 100.0° F. which ranged between 100.2° F. and 102.8° F. None demonstrated any evidence of infection. Of the six, only one was among the four who had shown an initial rise the preceding day; the temperatures of the other three had returned to normal.

As the heat wave continued unabated, eventually eighteen of the twenty-one boarders showed a rise in temperature; in some the rise was early and gradual, while in others the elevations occurred later and were more sudden in character. A temperature of 101.0° F. or above was registered at some time during the five-day heat period by seventeen patients. In seven cases the temperature rose to 102.0° F. or higher, and on one occasion a reading of 103.0° F. was recorded. There were no convulsions.

The heat wave began to recede on August 30, but the temperatures in this group remained elevated for an additional twenty-four hours before returning to normal. At no time could the rises in body temperatures be attributed to a cause other than the sustained, excessive heat.

The curve for the boarders (Fig. 1) shows the benign course followed by these patients on exposure to prolonged atmospheric heat, as compared with that of the cerebrally handicapped and those who were previously ill. Though their appetites were slightly dulled and their dispositions became moderately difficult, the boarders were at no time a nursing problem and never gave cause for concern.

Sex.—Sex had no significant influence upon the responses of these infants to the sustained environmental heat.

Age.—A comparison of the average temperatures for the three age groups revealed that the temperatures of the youngest were no more affected by the

heat than were those of the patients in the 1- to 2-year range. In agreement with Åkerren,[9] no conclusion could be drawn as to the stability of the heat-regulatory mechanism in very young infants as contrasted with that of older babies.

Race.—The white, Puerto Rican, Negro, and yellow races were represented. The average temperatures for the patients of each race showed a striking parallelism. This was unexpected since Dodd and Wilkinson[6] reported that in their series, the two Negro children had been unaffected by the heat, having remained playful throughout, despite having been in a room warmer than that occupied by the white patients. Figueras[15] and Kurrer[16] concluded that Negroes tolerate high external temperatures better than do whites, that they are less susceptible to sun and heatstroke, and therefore body temperature regulation is better in the Negro than in the white individual. Ferris and his collaborators[17] found that whereas the ratio of white to Negro patients among the general hospital admissions during the summer of 1936 was roughly 3:2, the ratio of white to Negro among the patients admitted for heatstroke during a heat wave that same year was 5:1.

Woodruff,[18] on the other hand, pointed out in 1912 that Negroes do not expose themselves in the tropics, and that when they migrate to very hot places they protect themselves with white clothes to prevent heat absorption or soon die. The same author cited a report in which of 146 cases of sunstroke, 13 were blondes, 20 were mixed skin types, and 113 were brunettes, indicating that the more dark-skinned individuals are more susceptible to the effects of heat than are the fair-skinned. He concluded with data from a veterinarian to the effect that in hot weather white horses, which reflect heat, rarely get thermic fever, the deaths being primarily among the animals of dark colors which absorb heat. More recently DuBois[19] showed, by means of a radiometer, that the differences between black and white skins are negligible so far as the radiation of heat is concerned, and that for all practical purposes one may consider the human skin, regardless of color, as a perfect black body radiator.

The small group of cases presented herein does not permit drawing conclusions as to the relative resistance to heat between white and Negro infants, but the impression received is that the Negro baby is no more immune to the effects of heat than is the infant of lighter skin.

From the data presented it may be concluded that healthy, normal infants up to 2 years of age may develop fever as high as 103.0° F. purely from the effects of high external temperatures. All such patients should be closely watched for several days after the recession of the heat wave, since the severe effects of exposure to heat may not appear until after the atmospheric temperature has fallen considerably.[8, 20]

EFFECT ON PATIENTS WITH CONGENITAL OR ACQUIRED CEREBRAL DAMAGE

The twenty-four patients with congenital or acquired cerebral damage consisted of eleven patients with hydrocephalus and/or spina bifida (of whom only one with spina bifida did not have an associated hydrocephalus), seven

Mongolian idiots, and one each of the following conditions: microcephalic idiot, achondroplasia, craniosynostosis, porencephalus, nonspecific birth injury and residual cerebral damage from a type 14 pneumococcal meningitis.

It was in this group that the most severe hyperpyrexias were encountered (Fig. 1). and it was these patients who posed the greatest nursing and medical problems. Despite the antipyretic measures enumerated one-fourth of these infants succumbed. There were no deaths in any of the other groups.

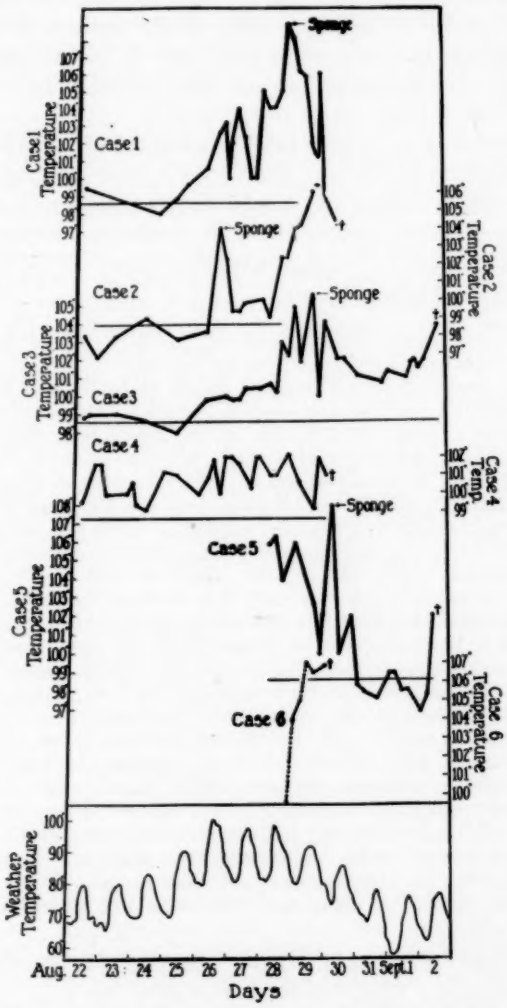

Fig. 2.—Individual temperature curves for six infants with cerebral defects who expired following exposure to sustained environmental heat.

As was the case with the well boarders, these patients had no temperature rise until after thirty-six hours of sustained heat. They were free from infections and had normal temperatures at the onset of the heat wave with the exception of the patient with the craniosynostosis on whom a craniectomy had been performed several days before, and the patient with birth injury who was recovering from an upper respiratory infection; in both the temperatures were rapidly returning to normal. On the evening of August 26, ten of the twenty-four patients showed elevations in body temperature above 100.0° F., with one as high as 104.0° F. Eventually all the patients in the group, except the microcephalic idiot, developed fever, and by the time the atmospheric temperature had subsided fifteen had had fever above 103.0° F.; one infant reached 109.0° F.

The individual temperatures of those who expired are shown in Fig. 2, and they give an indication of the wide excursions in body temperature sustained by those with cerebral defects. It is of interest to note that one of the two patients whose temperature rose to 108.0° F. or above survived the episode.

To correlate the thermal response with the clinical status, the case history of each fatality is briefly summarized.

CASE 1.—J. S., male, white, aged 15 months. Hydrocephalus, meningomyelocele, and paralysis of the lower extremities.

Multiple congenital deformities were found at birth, and the patient was admitted for custodial care at the age of 2 weeks. On admission there was hydrocephalus and a small perforation of the meningomyelocele from which cerebrospinal fluid escaped. Several days after admission the temperature rose to 104.0° F. and was attributed to infection of the meningomyelocele. During the third month of life the spinal defect was repaired surgically. Following this the hydrocephalus expanded rapidly. From the eighth to the tenth month there was periodic, unexplained fever, and the possibility of cerebral fever was entertained. Subsequently, the infant became spontaneously afebrile and followed an uneventful course until the onset of the heat wave. On the second day of sustained heat his temperature gradually rose to 103.0° F. Over the next two days there were wide temperature excursions which responded to aspirin and sponging only temporarily. On the fourth day of the heat wave his temperature rose to 105.0° F. and then to 109.0° F.; the patient appeared dry, pale, and was comatose. Simultaneously there were generalized fine clonic movements. Sweating was absent and the respirations were labored. Despite the repeated sponging and administration of aspirin, the temperature fell to 104.0° F. only briefly, promptly rising to 108.0° F., at which time the convulsions and gasping respirations returned. Physical and laboratory examinations were negative. The following day his temperature was 101.0° F. but rose to 106.0° F. a few hours later. Although sponging was discontinued when 102.0 F. was obtained, his temperature continued to fall. Twelve hours later a body temperature of 97.2° F. was registered and the patient expired shortly thereafter.

CASE 2.—S. B., female, white, aged 3 months. Hydrocephalus, lumbar meningomyelocele, and paralysis of the lower extremities.

The patient was admitted in May, 1948, at the age of 1 week, for evaluation regarding the advisability of surgical intervention for a meningomyelocele. When surgery was deemed inadvisable, she remained in the hospital for custodial

care. Development was slow and definitely retarded in all respects. Enlargment of the head progressed and the lower limbs showed early atrophy. The course was otherwise uneventful until thirty-six hours after the onset of the heat wave, when the temperature suddenly rose to 104.0° F. There was no evidence of acute or chronic infection. The temperature promptly responded to aspirin and sponging, remained normal for about twenty-four hours, and then started upward again. Despite active antipyretic therapy it continued to rise until 106.0° F. was reached on the fifth day of the heat wave, when the patient expired.

CASE 3.—R. J., male, white, aged 18 months. Residual cerebral damage from type 14 pneumococcal meningitis.

The patient had been normal until the tenth month of life when, after an illness of three weeks, he was admitted in January, 1948, and a diagnosis of pneumococcus type 14 meningitis and septicemia was made. Despite intensive chemotherapy, type specific antiserum, etc., the patient remained acutely ill for some thirty days. Finally spinal fluid cultures became sterile and the convulsions which had been present from the onset ceased, but the patient showed evidence of spastic quadriplegia and required feeding via gavage tube. A pneumoencephalogram done on the forty-eighth hospital day revealed massive ventricular enlargment. Until his death, the patient's existence was a vegetative one; all growth and development ceased and feedings could be taken only by gavage. Up to his fifth month in the hospital there were frequent spiking fevers which did not respond to chemotherapy or aspirin, being reducible only by means of sponging or ice water enemas. After the fifth month (May, 1948) the course was afebrile but otherwise unchanged.

Through the third day of the heat wave the patient retained a normal body temperature, but during the next two days his temperature rose abruptly, being only temporarily reduced by repeated sponging and salicylate therapy and reaching 105.8° F. There were no convulsions and the physical examination was noncontributory. As the weather heat subsided, the patient's temperature ranged between 100.0° F. and 102.0° F. for several days. Then on September 2, three days after the return of normal environmental conditions, the temperature rose to 104.0° F. and the patient expired.

CASE 4.—Jn. St., male, white, aged 8 months. Hydrocephalus, meningomyelocele, talipes equinovarus, and paralysis of the lower extremities.

The patient did well until the third day of life when he developed Cheyne-Stokes respirations, refused feedings, and had a temperature ranging between 100.0° F. and 106.0° F. A diagnosis of subdural hematoma was made and was confirmed when the patient was transferred to Bellevue Hospital. Cerebrospinal fluid cultures were sterile. Within a few days the condition improved and a relatively uneventful course followed. There were two episodes of respiratory distress which followed closely upon feeding and were considered due to aspiration. The head circumference increased rapidly in size for the first few months. On occasion a temperature of about 101.0° F. would persist for several days with no apparent reason; subsidence was always spontaneous. Just prior to the onset of the heat wave the patient had apparently entered upon a similar episode with temperature ranging between 99.2° F. and 101.2° F. As the environmental temperature rose and persisted, the patient became restless but showed no appreciable further elevation of temperature. On August 30 his temperature was 102.0° F.; he was cyanotic and was convulsing. He expired within a few moments. Inasmuch as this occurred shortly after feeding and no permission for necropsy was granted, exitus from aspiration cannot be ruled out though no untoward incident was noted during the feeding.

CASE 5.—L. L. female, white, aged 15 months. Mongolian idiocy.

This seriously retarded infant had always been very irritable, but in the two days preceding admission (third and fourth days of the heat wave) had become markedly more so. She had had frequent bouts of unexplained fever since birth, but with this illness the fever was higher than usual; she took food and fluids poorly, and had repeated tonic seizures. On the fifth day of the heat wave she was admitted to the hospital in coma with a temperature of 104.8° F., marked intermittent nuchal rigidity, noisy respirations, dullness over the right upper chest anteriorly, and coarse rhonchi throughout all lung fields. The skin was hot and dry. All laboratory findings were within normal limits. There was no reduction in body temperature despite intensive therapy throughout the ensuing twenty-four hours. On the following day there was extensive impairment of the percussion note and profuse moist râles bilaterally. Then there was a transient temperature fall to 100.0° F. which was followed by an abrupt rise to 108.0° F. with concomitant tonic and clonic convulsions, cyanosis, and coma. Continuous sponging finally succeeded in reducing the fever. With the return of normal environmental temperatures, the patient's temperature remained at normal and subnormal levels for forty-eight hours though she never roused from the stuporous state. On September 3, the temperature suddenly rose to 102.0° F. and the patient expired.

CASE 6.—J. G., female, white, aged 8 months. Mongolian idiocy, left chronic otitis media.

The patient had been well until the day before admission, which was the fourth day of the heat wave, when a high fever appeared with rapid respirations and a slight cough. She took food and fluids poorly. On the morning of admission, August 30, her temperature was 106.8° F.; she appeared acutely ill, and her respirations were 120 per minute. The fontanel was slightly sunken, the mucous membranes were dry, and the left eardrum was retracted. The chest was dull over the right base anteriorly and many small inspiratory râles were heard over the same area. The liver edge was palpable 2½ cm. below the costal margin. The skin over the upper chest and arms had a fine, diffuse miliaria-like eruption, and was hot and dry. There were no convulsions. A hypodermoclysis of 100 c.c. 3 per cent glucose and 0.3 per cent sodium chloride solution was immediately given and 1 gr. of aspirin was administered. Before the therapy could have effect, the patient died.

At autopsy the pertinent findings consisted of dilatation of all the chambers of the heart and interauricular and interventricular septal defects; the entire left lung and the right lower lobe were firm and reddish-blue with gray and dark red patches. On pressure moderate amounts of clear fluid could be expressed. Microscopic examination of the lungs showed marked congestion of the alveolar capillaries with patchy outpouring of red blood cells and edema fluid into the air spaces. Within the air spaces there were large numbers of mononuclear and multinuclear giant cells. There was a moderate degree of fatty change in the liver cells, most marked in the periportal areas and diminishing toward the central vein. The sinusoids were somewhat distended and filled with blood. The splenic pulp was congested and there was an increase in the total number of polymorphonuclear leucocytes. The adrenal cortical cells were pale and not well vacuolated. At the corticomedullary junction and within the medulla there was evidence of fresh hemorrhage.

The pathologic diagnosis was: Mongolian idiocy, congenital heart disease, congestion and edema of the lungs with hemorrhagic lobular pneumonia, fatty change and congestion of the liver, chronic passive congestion of the spleen and hemorrhage into the adrenal medulla.

There is no striking difference in the incidence of thermal fever among the boarders and the infants with cerebral damage. What is arresting, however, is the marked contrast in the character and intensity of the thermal responses of the two groups, and the absence of fatalities in the one group and the death of one-fourth of the patients in the other. Poikilothermia in the presence of cerebral damage in infants has been reported by several authors.[9, 21, 22] There is experimental evidence to indicate that hydrocephalus predisposes to altered function of the thermoregulatory center. Bazett and Penfield,[23] in 1922, showed that following decortication, cats retain no temperature control. If the decortication is unilateral the thermoregulatory center remains unaffected; but if, in these unilaterally decorticate cats, the remaining brain matter is subjected to some pressure (i.e., wax), the raised intracranial pressure readily destroys the power of temperature control.

Åkerren[9] emphasized the marked tendency of infants "stigmatized" in some way by congenital or acquired morbid conditions such as mongolism, spasticity, hydrocephalus, etc., to develop highly febrile reactions to infections, and concluded that hyperpyrexia may be both a cause and a result of cerebral injuries.

The evidence for pneumonic involvement in two of the six fatalities might raise the question of the validity of attributing these deaths to the excessive heat. However, it has been pointed out[9] that although the combination of dyspnea, cyanosis, pallor, and very high fever simultaneous with catarrhal symptoms would suggest a severe pulmonary infection such as capillary bronchitis or bronchopneumonia, the actual pulmonary involvment may prove to be extremely meagre. The same author continues that the unfavorable effect which hyperpyrexia has on the organs of respiration and circulation, especially in the presence of convulsions and coma, is likely to favor the appearance of grave affections of the air passages, especially if the patient has already suffered from an infection of the upper passages or pharynx. In a patient with severe involvment of the air passages associated with hyperpyrexia, it does not necessarily follow that the high fever is secondary to the respiratory pathology; the causal relation may be the reverse. Some authors[19, 20, 24] have reported that the post-mortem examination of patients who died of heatstroke almost always reveals chronic congestion and edema of the viscera, especially of the lungs and brain. Horanyi-Hechst[25] found that in simple deaths from heat as it occurs in cases of heatstroke or in experimental overheating of animals, severe cerebral symptoms in the form of loss of consciousness, paralysis, convulsions, hyperpnea, and tachycardia are characteristic; at autopsy the animals demonstrated hemorrhages and hyperemia in both the meninges and the vessels of the brain substance. McKenzie and LeCount,[26] in their post-mortem studies on thirty-seven patients who died of heat stroke, found the following quite regularly: edema of the brain and/or leptomeninges with associated hyperemia of the lungs, lessened substance of the suprarenal cortices, hyperplasia of the spleen, cloudy swelling of the liver, the kidneys, and myocardium, and petechial hemorrhages of the mucous membranes and of the skin. It has also been reported,[27] however,

that pneumonia of the upper lobes is one of the commonest predisposing factors in the development of hyperpyrexia in excessively hot weather.

In the light of these findings, therefore, it is not unwarranted to conclude that the external heat was the primary causative element in the deaths of these infants.

EFFECT ON PATIENTS WITH DIARRHEA

There were three patients who had diarrhea during the period of the heat wave. In two of these, the diarrhea was associated with an otitis media and an upper respiratory infection. Stool cultures were repeatedly negative for intestinal pathogens. Prior to the onset of the heat wave (August 22 to 24), these patients had two to six bulky, watery, yellow stools a day, were afebrile, and only slightly dehydrated. They all showed a moderate degree of weight loss. Penicillin and sulfadiazine were given as indicated. Following the suggestions of Chung and Viscorova,[28] feedings were given as tolerated throughout the course of the illness. The oral feedings and supplementary parenteral fluids were given in amounts which insured a total daily intake of approximately 200 c.c. fluids per kilogram per day. The total fluids were calculated to supply the patient with from 2 to 3 Gm. of sodium chloride per day and an adequate amount of potassium.

Table I shows the actual fluid intake (in cubic centimeters) of these patients during the days indicated. Any vomitus has been estimated and deducted from the total intake. In general the fluid intake was adequate.

TABLE I

PATIENT	WEIGHT (LBS.)	8/24	8/25	8/26	8/27	8/28	8/29	8/30
M.M.	14	---	420	1420	1370	1330	1160	840
G.R.	11	840	720	1320	900	1280	750	1110
M.O.	5½	440	560	720	900	820	255	450

In contrast to the others in this series, the patients with diarrhea showed a sudden rise in body temperature within twelve hours of the onset of the heat wave, for an average reading of 101.6° F. on the evening of August 25. Their clinical condition rapidly deteriorated though there was no evidence of a superimposed infectious process. They appeared cachectic, dehydrated, and their stools became projectile and increased in number and volume. In one patient (M.M.) vomiting appeared for the first time and, because of its severity, oral feedings were withheld. Little or no response was noted upon intensification of the antipyretic and fluid therapy.

On the fourth day of the heat wave 1 Gm. of sodium chloride was added to the formulas of these patients as well as to the others. All three took their formulas well, including the patient whose vomiting had previously been quite serious. The following day, approximately thirty hours after instituting the extra gram of salt, all three patients showed a dramatic drop in fever and general improvement despite the continued heat and no further change in therapy. (Fig. 3.) The number and character of the stools improved from this time on; the patients ceased to be the serious problem they had been, and went on to uneventful recoveries.

Summer diarrhea in infants has long been recognized as a definite, though somewhat nebulous, entity. Abt[2] commented that children who have suffered frequent insults from gastrointestinal diseases during the summer are liable to acute exacerbations of intestinal intoxication associated with high fever and marked losses of weight. This is understandable since the younger child tolerates water loss less well than the older child, and the combination of fever, poor fluid intake, and diarrhea readily lead to an anhydremia which is most difficult to treat. It has been shown[29] that as the temperature range or mean temperature rises above its ordinary summer level, there is likely to be a rise in the diarrhea and enteritis infant mortality rate.

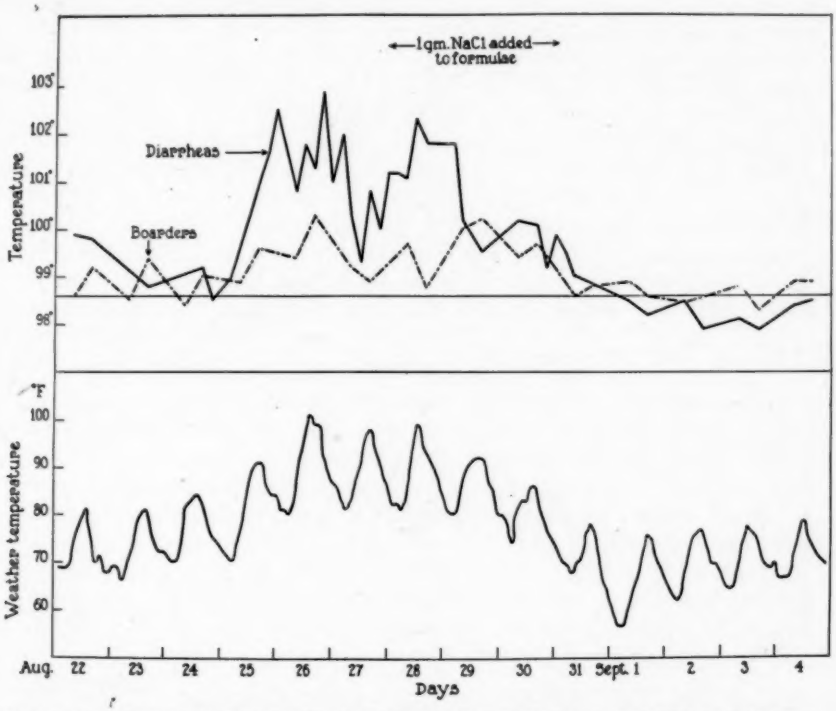

Fig. 3.—A comparison of the temperature responses of well infants and infants with diarrhea during the heat wave (Aug. 25 to 29, 1948).

The average temperature curve for those with diarrhea differs markedly from that of the remainder of the patients. Their temperatures rose within twelve hours of the onset of the heat wave, whereas the other patients showed no rise until after approximately thirty-six hours of sustained environmental heat. This observation suggests that in diarrhea the state of anhydremia makes the patient especially susceptible to the effects of atmospheric heat, inasmuch as this added factor unduly taxes the already faltering thermoregulatory mechanism. Consequently, as for all the previously discussed patients, strenu-

ous efforts must be instituted early to prevent the additional influence of heat on patients with diarrhea.

Of particularly interest is the fall in body temperature and general clinical improvement which occurred within thirty hours of the institution of additional salt. Several investigators[19, 30] have reported that since the blood sodium chloride levels are normal in cases of heatstroke, and that there is failure to respond to saline administration,[31] salt dissipation or need plays little if any part in the syndrome. Miller,[32] on the other hand, believes it is reasonable to assume that since the largest part of the approximately 100 Gm. of sodium chloride in the average (adult) human body is to be found in the extracellular compartment, a considerable amount of chlorides can be lost without a corresponding lowering of the blood chloride level which the organism tenaciously attempts to maintain.

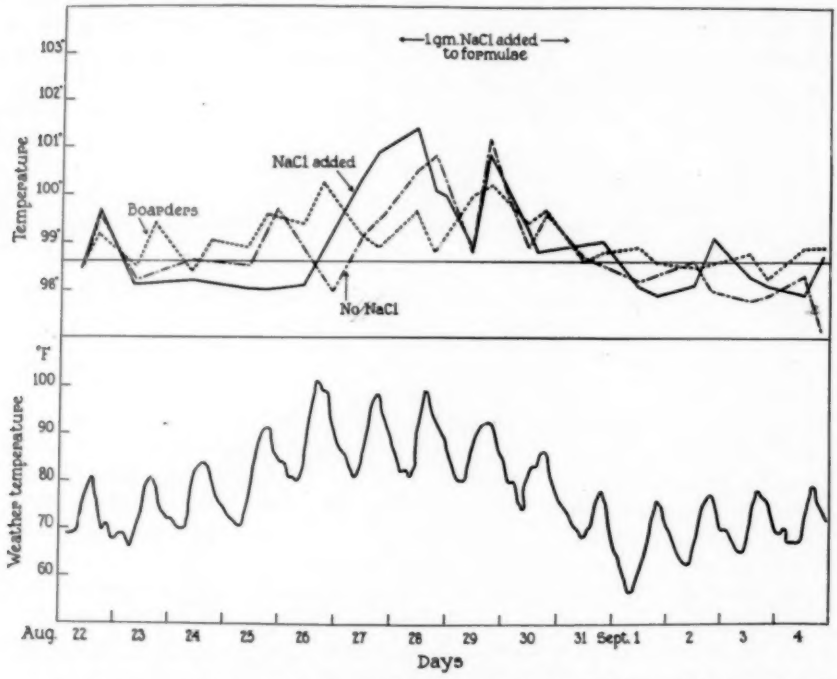

Fig. 4.—A comparison of the temperature responses of well infants, infants with primary pulmonary tuberculosis to whose formulas 1 Gm. sodium chloride was added, and infants with primary pulmonary tuberculosis to whose formulas no sodium chloride was added.

The febrile course of the patients without diarrhea to whom additional salt was administered was unaffected. A comparison between two patients with primary tuberculosis who received additional salt and two similar patients who received no salt reveals no difference in the intensity and type of temperature curve traced. (Fig. 4.)

The significant fall in body temperatures in those with diarrhea when the temperatures of the other patients were still markedly elevated suggests a beneficial effect from the additionl salt in this condition. However, no further conclusions may be drawn until further and more extensive studies are carried out.

EFFECT ON MISCELLANEOUS DISEASES

There was a total of sixteen patients in this group which included conditions such as primary pulmonary tuberculosis, miliary tuberculosis, tuberculous meningitis, bronchopneumonia, congenital lung cyst, chronic eczema, spinal deformity, erythroblastosis fetalis, inguinal hernia, congenital cataracts, congenital torticollis, Letterer-Siwe's disease, and omphalitis.

As a group, they showed febrile responses to the environmental heat midway between that of the patients with cerebral damage and that of the well boarders. The character of the average curve was similar to that of the other two groups (Fig. 1). It is of interest that the highest fevers were found in the patients with the infected congenital lung cyst and with bronchopneumonia. The remainder of the patients, whose afflictions were essentially of a chronic nature, developed fevers which were, in general, slightly lower.

From the findings in this group it may be concluded that in the presence of pre-existing pathology which is not cerebral in origin the thermal response to sustained environmental heat will be somewhat higher than that encountered in previously healthy infants, but well below that of patients who have diffuse cerebral damage.

THERAPY

It is quite obvious that for cerebrally handicapped patients strenuous measures must be taken to forestall the development of hyperpyrexia during heat waves. To await its development to institute therapy may be disastrous, for once the body temperature in these patients begins to rise, all efforts will prove futile in a large percentage of the cases. If it is not feasible to remove these infants to a cooler environment, more normal surroundings must be created for them by the use of fans, ice, frequent cool baths, etc. In addition, any pre-existing infection must be vigorously combated and brought under control at the earliest possible time. Similarly, steps must be taken to prevent exposure to individuals who harbor acute infections, especially those of the respiratory tract.

If the body temperature has already risen every effort should be made to promote heat loss. Of primary importance is the reduction of the environmental temperature, which may be accomplished by the various methods already suggested. Also, the clothing should be completely removed and 1 gr. of aspirin should be administered every four to six hours. These measures should be instituted promptly and continued as long as the environmental temperature remains elevated and for several days thereafter.

Although stressed for those with cerebral damage, the measures outlined should be applied to all infants, normal as well as diseased, during periods of sustained heat.

DISCUSSION

The data presented indicate that the majority of infants under 2 years of age will develop fever when exposed to sustained atmospheric heat. The intensity of the fever depends upon the individual patient's state of health prior to the exposure. The thermoregulatory apparatus of the normal infant, though labile, is capable of withstanding prolonged excessive heat and of protecting the individual from its effects. However, where there exists severe functional or organic brain damage, the heat-regulating center is unable to cope with the demands imposed upon it, and heatstroke frequently ensues. Whether the defect lies in the vasomotor system[31, 33-38] in the sweating mechanism,[19, 31, 38-47] or primarily in the central heat-regulating organ, the hypothalamus,[48-54] cannot be said. It is known, however, as Sutton[55] pointed out in 1909, that once the mechanism of heat regulation in the human body has been definitely upset by high external temperature, a vicious cycle is established. When the internal temperature rises, the processes of oxidation (in accord with van't Hoff's law), and therefore the production of heat, also increase, so that the body temperature rises still further, and so on. Consequently, the main problem lies in preventing the initiation of such a cycle.

If it is assumed that the factors of heat production (activity, basal metabolic rate, and calorigenic action of food) were similar for all patients, and since the amount of heat lost to the surroundings by convection and radiation was the same because of exposure to identical environmental conditions, there remains but one factor for heat dissipation where individual variations may have accounted for the vast differences in body temperatures. That factor is sweating. Unfortunately, no records were kept of which patients perspired and which did not, and consequently no comment can be made on the subject, but it seemed to be the general impression that sweating was least observed among those with the highest body temperatures. Investigations along these lines are being planned at present.

SUMMARY

A clinical study of the thermal responses of eighty-eight patients under 2 years of age was made during a five-day heat wave in New York City in the summer of 1948. The following conclusions were drawn:

1. In the majority of infants under 2 years of age, the body temperature rises when exposed to sustained environmental heat.

2. This elevation may exceed 103.0° F. in normal, healthy infants (including mature newborn infants), in the absence of any evidence of acute infection.

3. Under 2 years of age there is no apparent correlation between age, sex, or color and the susceptibility to develop thermal fever.

4. Usually there is a lag phase of thirty-six or more hours from the onset of the atmospheric heat to the rise in body temperature. Similarly, the fever may not subside until twenty-four or more hours after the external temperatures have returned to normal levels.

5. Patients with diarrhea seem to develop fever sooner than normal or otherwise ill infants. It is suggested that additional alimentary salt may be beneficial in restoring the body temperature of infants with diarrhea to normal levels.

6. A pre-existing acute or chronic infection, especially of the respiratory tract, predisposes to the development of high fever upon exposure to sustained environmental heat.

7. In infants with congenital or acquired cerebral defect, there exists a marked tendency to the development of hyperpyretic states and to heat stroke. The temperature may rise to 109.0° F. and the mortality is high.

8. These fevers are exceptionally resistant to antipyretic measures once they become established. Consequently, prevention is the keystone of successful therapy.

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ILLNESSES WITHIN THE FIRST YEAR OF LIFE

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ALTHOUGH the morbidity rate is said to be highest in the first year of life, few articles in the literature supply definite information about illnesses in this period. The purpose of this paper is to present data obtained in a study of illnesses that occurred among 417 infants during their first year of life.

Illness was interpreted as a continuous period of "infection" regardless of complication. This definition ruled out such conditions as infantile colic, injuries, operations, the more simple dermatologic conditions, and congenital defects such as clubfeet. If one condition was reported as the primary cause and was associated with other conditions, only the primary cause was tabulated. If there was more than one cause of illness, the disease most specifically associated with the period of sickness was preferred over a minor condition which preceded or accompanied it. Records obtained in this manner were of the incidence of attacks rather than of illnesses in the sense of chronic ill-health.

The infants in this series were born of residents of Rochester, Minn., during 1944 through 1946. Owing to the uniquely coordinated program of medical care for children in this city, most of the infants are seen at a well child clinic each month during their first year of life. For their more serious illnesses most of these children are attended by a pediatrician. To be assured that the information concerning the illnesses was collected from the infants' mothers at frequent intervals, only those infants were selected who had attended the Well Child Clinic at least nine times during their first year of life. At each of these conferences with the mother, the physician inquired about any illnesses that the child might have had since his last visit, and recorded the diagnosis, approximate date, and whether a physician attended the child during the illness. As a check that all illnesses were reported, the pediatricians' records on these children were reviewed and a record of any additional illnesses was inserted. This selection of infants does eliminate the few children who were chronically ill and needed prolonged care by a pediatrician, or who might have died before the end of the first year, but we have included any illness that was observed by the mother, no matter how mild.

Among this group of 417 infants there were recorded 679 illnesses, which were distributed equally between the boys and the girls. This is not in agreement with the illness study by Collins,[1] who found the illness rates for males to be consistently greater than those for females except in the age period 1 to 2 months. Data for his study were obtained from five different illness studies conducted by periodic canvasses of families within the past twenty-five years.

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In each survey the families were visited at intervals of two to four months, and a record was made of any illness of the infants under observation by month of age up to twelve months. Falk and his associates[2] had found in a public health survey that illnesses in the first fifteen years of life were equally distributed between the two sexes. Illness was defined by Falk as "any disorder that wholly or partially disabled an individual for one or more days or as an experience for which medical service of any kind is received. Any condition, symptom or disorder for which drugs costing fifty cents or more are purchased is considered an illness."

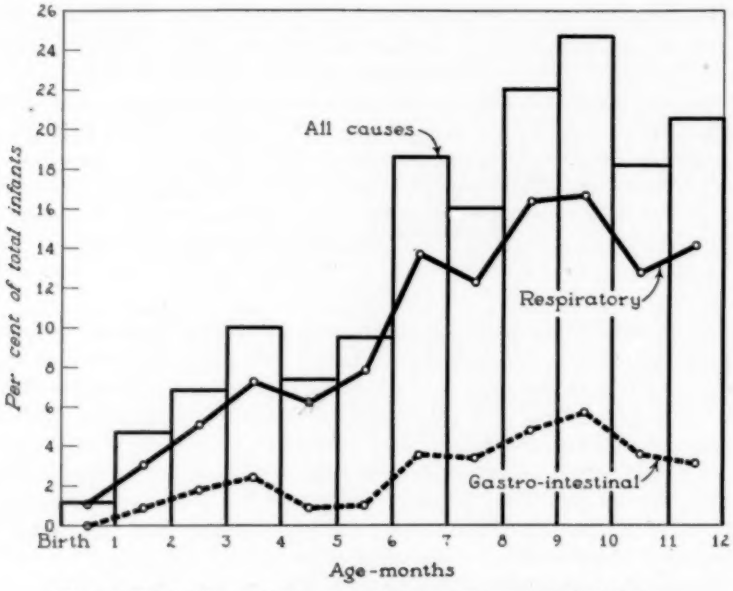

Fig. 1.—The incidence of illness in relation to the age of the infant.

The incidence of illness for this group of infants was 1.63 per infant for the age period studied. This is a higher incidence of illness than was found by Falk and his associates, Collins, or Sydenstricker,[3] but lower than Stevenson[4] reported. Falk found that the incidence rate of illness during the first year of life varied between 1.29 and 1.39 per infant depending on the income level of the families. Collins found an illness rate of 1.45 per person for infants less than 1 year of age. In the Hagerstown morbidity study,[3] the rate was 1.59 per person for children less than 5 years of age. Stevenson found among 263 infants in Boston, who were carefully followed in a longitudinal study of child health and development, that the average number of infections per infant varied from 1.79 to 2.43 per year according to the method of feeding. Some variations in the reported incidence rate of illness can be accounted for by different definitions of illness, the variety of income groups surveyed, the geographic location of the subjects, and the ages of the individuals observed.

Of the 417 infants in this series, 22.8 per cent were reported as not being ill during their first year of life, 28.5 per cent had one illness, 26.2 per cent had two illnesses, and 22.5 per cent had three or more. Among nearly 40,000 persons of all ages, Collins found that 48 per cent did not suffer from illness during a year, 32 per cent were ill once, 13 per cent twice, and 7 per cent three or more times. Similar figures were obtained by Falk and his associates from a study of members of 9,000 white families in seventeen states.

The distribution of illnesses according to the age of the infant is shown in Fig. 1. There is a steady rise in the number of illnesses from all causes as the infants approach their first birthday, as well as in the illnesses due to respiratory and gastrointestinal disease. The illnesses during the last six months of the first year are approximately three times the number during the first six months of life; this increase is of the same order among the respiratory and the gastrointestinal diseases. Grulee and his associates[5, 6] investigated the morbidity from infections among 20,000 artificially-fed and breast-fed infants who were followed for as long as nine months by Chicago's Infant Welfare Society during 1924 to 1929. They found a rise in the illness rate each month until the fifth month with all types of infant feeding; the rate then decreased in the breast-fed and partially breast-fed groups but in the artificially-fed group the rise continued through the ninth month. Collins found that illnesses from all causes start with a high rate for the first month of life and drop to the lowest rate in the second month, followed by a gradual increase to a level of about 1.5 illnesses per infant throughout the last half of the first year of life. The digestive diseases had a high rate in the first month of life; then the rate fell rapidly and remained quite stable throughout the first year, while the respiratory diseases increased during the period observed.

It has been generally recognized that respiratory infections and gastrointestinal illnesses are the principal causes of illness in this age period. In Table I are shown the illnesses during the first year of life. In this group respiratory

TABLE I. CAUSES OF ILLNESS WITHIN THE FIRST YEAR OF LIFE

	CASES	PER CENT OF TOTAL
Respiratory diseases	495	72.9
Coryza, "cold," pharyngitis, tonsillitis, and upper respiratory infection	388	57.1
Otitis media with respiratory infection	36	5.3
Laryngitis	12	1.8
Bronchitis	42	6.2
Influenza	13	1.9
Pneumonia	4	0.6
Gastrointestinal diseases	130	19.1
Diarrhea	93	13.7
Gastroenteritis	37	5.4
Contagious diseases	29	4.3
Chickenpox	9	1.4
Rubella	7	1.1
Whooping cough	6	0.9
Rubeola	3	0.4
Poliomyelitis	3	0.4
Mumps	1	0.1
Roseola infantum	19	2.8
Other	6	0.9

disease was the most frequent and accounted for 72.9 per cent of the illnesses. Coryza, "cold," and infections of the respiratory tract comprised almost 86 per cent of the respiratory illnesses. In Sydenstricker's[7] report of illnesses among a general population group, 61 per cent were due to respiratory infection. Holland[8] found that minor respiratory and acute communicable disease accounted for three-fourths of the illnesses of children aged less than 15 years. Gastrointestinal illnesses were next in frequency and comprised 19.1 per cent of the total number of illnesses. The latter were all cases of quite mild diarrhea and gastroenteritis, and none of the infants required hospital care. Communicable disease caused 4.3 per cent of the illnesses, chickenpox and rubella being the most frequent. Since there was such a small number of communicable diseases the rates cannot be compared with those in Godfrey's,[9] Holland's,[10] and Collins's[11] studies. Roseola infantum was the diagnosis in 2.8 per cent of the illnesses and other diseases accounted for 0.9 per cent.

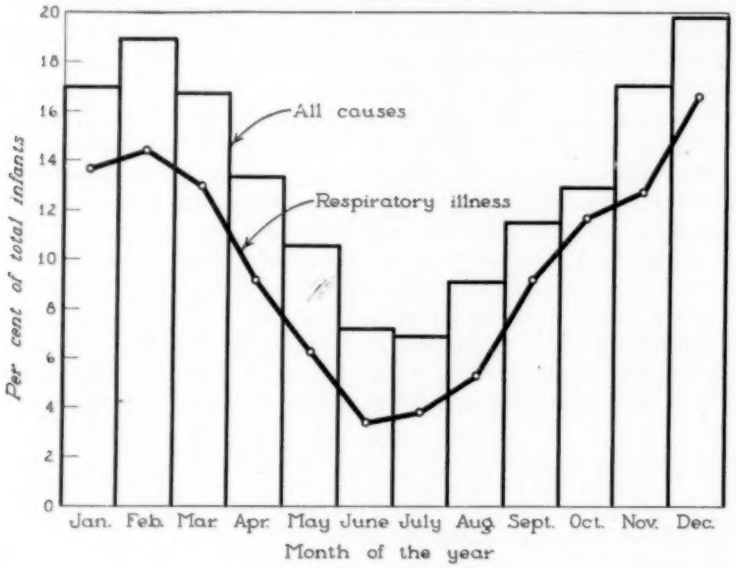

Fig. 2.—Seasonal incidence of illness.

A seasonal variation in the incidence of infection was expected and this tendency is clearly shown in Fig. 2. The rate of the respiratory illnesses follows closely the frequency of total illnesses throughout the entire year. The peaks for both were in December and February and the lowest levels were in June and July. Since there was no seasonal fluctuation in the rate of the gastrointestinal illnesses in this group of infants, it was not depicted in the graph.

In Grulee and his associates'[12] study the respiratory infections were greatest in the spring and the gastrointestinal disturbances were highest in the summer.

TABLE II. THE DURATION OF BREAST FEEDING IN RELATION TO THE RATE OF ILLNESS

DURATION BREAST FEEDING (MO.)	INFANTS	ILLNESS RATE				TOTAL
		BIRTH-6 MO.		6-12 MO.		
		ALL CAUSES	RESPIR-ATORY	ALL CAUSES	RESPIR-ATORY	
0	55	0.33	0.27	0.83	0.58	1.16
Less than 3	202	0.49	0.37	1.34	0.98	1.83
3-5	59	0.37	0.31	1.14	0.73	1.51
6-8	73	0.32	0.25	1.25	0.88	1.57
9+	28	0.32	0.25	1.18	0.93	1.50

Much has been said concerning the influence of breast milk on morbidity in this age period. Grulee and his associates[5, 6] found lower morbidity and mortality rates among breast-fed and partially breast-fed infants than among the artificially-fed infants. Stevenson found a significant difference between the average number of respiratory infections in breast-fed and in artificially-fed infants but not in the number of gastrointestinal and other infections. However, Stevenson found no significant difference between the number of respiratory infections per infant in the breast-fed and the artificially-fed groups within the first six months of life but he did find a difference in the second six months of life. In Table II it is shown that the duration of breast feeding among the 417 infants did not influence the rate of incidence of all types of illness and respiratory infections per infant within the first year of life. The illness rate for the breast-fed babies (1.69 ± 0.07 per infant) was significantly higher than the rate for those (1.16 ± 0.16 per infant) who were never put to breast at any time. This increased incidence for illness occurs during the second six months of life and is directly opposite to the conclusion reached by Stevenson. Respiratory illness showed a similar pattern. However, many other factors may influence the number of illnesses noted. Ebbs and his associates[13] found that the incidence of illness in babies up to the age of 6 month and the number of deaths resulting from these illnesses were many times greater in the group whose mothers had poor prenatal diets. The supplementary diet of mothers during breast feeding and the diets of the infants, exposure to older children and adults, and housing conditions, are possible factors in the incidence of illness. These factors may obliterate the influence of breast feeding.

SUMMARY

Among 417 infants observed for attacks of illness within their first year of life, the incidence of illness was not influenced by sex.

The incidence of illness was 1.63 per infant per year.

The frequency of illness increased as the infants approached 1 year of age. There was a definite seasonal fluctuation in the incidence of respiratory illnesses but not in the incidence of gastrointestinal illnesses.

Respiratory illnesses comprised nearly 73 per cent of the illnesses during the first year of life.

From a statistical standpoint the duration of breast feeding did not influence the rate of illnesses for the period studied. However, it must be remembered that many other factors predisposing to illness may have obliterated this single influence.

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TREATMENT OF PERTUSSIS WITH POLYMYXIN B (AEROSPORIN)

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POLYMYXIN is a new antibiotic which in laboratory studies is active against a wide variety of gram-negative organisms. Benedict and Langlykke[1] first reported the antibiotic properties of crude extracts of *Bacillus polymyxa*. Shortly thereafter Ainsworth and associates[2] described the chemotherapeutic activity of a relatively pure extract which they derived from *Bacillus aerosporus* and which they called "aerosporin." Stansly and associates[3] independently reported on the antibiotic activity of *B. polymyxa* and named the active principle "polymyxin." It was soon found that *B. polymyxa* and *B. aerosporus* were identical organisms and at a recent conference* on antibiotics derived from this bacteria it was decided that all further derivatives would be called polymyxin. Differentiation was to be made by use of lettering such as Polymyxin A, Polymyxin B, etc. Schoenbach and his associates[4] have continued the experimental and clinical investigations with the polymyxin described by Stansly (designated Polymyxin D). Aerosporin has been further purified and the new antibiotic is known as Polymyxin B. Polymyxins B and D apparently differ not only in biochemical properties but in therapeutic and toxic effects as well.

In a recent publication, Brownlee and Swift[5, 6] reported their results with the use of aerosporin in the treatment of pertussis, and concluded that this extract had a definite therapeutic value. Toxic effects were noted, but these were transient, and it was felt that they were due to impurities. Because of these suggestive results and with the production of the purified aerosporin product, Polymyxin B, we decided to treat a series of patients with pertussis with this new antibiotic.

METHODS AND MATERIALS

Eighty-four patients with pertussis were treated with Polymyxin B from August to November, 1948, at Willard Parker Hospital; sixty-six by the intramuscular route, and eighteen by aerosol inhalation (Table I). The diagnosis

TABLE I. THE EIGHTY-FOUR INVESTIGATED PATIENTS WITH PERTUSSIS TREATED WITH POLYMYXIN, ACCORDING TO AGE AND METHOD OF TREATMENT

SIXTY-SIX PATIENTS TREATED INTRAMUSCULARLY				
Ages	0-6 mo.	7-12 mo.	1-2 yr.	2 yr. and over
No. of patients	19	10	10	27
EIGHTEEN PATIENTS TREATED BY AEROSOL INHALATION				
Ages	0-6 mo.	7-12 mo.	1-2 yr.	2 yr. and over
No. of patients	4	6	1	7

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This study was aided by a grant from Burroughs Wellcome and Co., Tuckahoe, N. Y., who also supplied Polymyxin B.

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in all cases was substantiated by bacteriologic or hematologic studies in addition to the history and clinical findings. Admission roentgenograms of the chest were taken on all patients, were repeated routinely after treatment, and were taken again whenever clinical signs indicated pulmonic complications.

Because previous workers using polymyxin reported kidney toxicity, daily urinalyses were done on all patients while under treatment and for three days thereafter. Serial nonprotein nitrogen levels were taken during the course of treatment on the first twenty patients.

Polymyxin B was supplied in ampules as a dried, colorless hydrochloride, each ampule containing the equivalent of 40 mg. of polymyxin. A dried sulfate preparation equivalent to 50 mg. of Polymyxin B per ampule was also given to a few patients toward the end of the study. Sterile saline was used as the diluent.

The intramuscular dosage was 0.8 mg. per kilogram of body weight every four hours (4.8 mg. per kilogram per day). This dosage was given for five consecutive days, as previously suggested by Brownlee and Swift.[4, 5] The hydrochloride solution caused pain about the site of injection in all patients. A sulfate preparation causing less local irritation was used in a few patients. None of the reactions resulted in necrosis.

When the drug was administered by the aerosol method, 60 per cent of the estimated intramuscular dose was divided into four doses: at 9 A.M., 1 P.M., 5 P.M., and 9 P.M. The Vaponephrin plastic nebulizer* was used and saline was added to each individual dose, so that 2 c.c. of fluid containing the polymyxin was always given. The nebulizers were checked so that it always took at least ten to fifteen minutes for each aerosol procedure. After every treatment 1 c.c. of saline was added to the nebulizer to wash out the precipitated drug. In general, about 3 to 4 L. of oxygen per minute provided sufficient vaporization and the desired length of treatment. Infants below 8 months of age were usually placed in plastic hoods for aerosol therapy. For older children cones were made from discarded roentgenographic film, and these cones were placed about the nozzle of the nebulizer with the wide end being held gently over the nose and mouth. Blood levels obtained with both methods of administration indicated good absorption.

Patients with evidence of bronchopneumonia or convulsions were not treated with polymyxin. Since the therapeutic efficacy of this drug had not been proved, it was felt unjustifiable to deny these critically ill patients hyperimmune serum and other therapy. For this reason we could not use alternating controls. We did not feel that selected controls would be of any value because of the difficulty in obtaining two groups of similar age and comparable severity and length of illness.

The patients treated with polymyxin received no other medication except for a few that had been given sulfonamides prior to admission. The general management of the patients was essentially as outlined by the co-authors in a previous publication.[7]

*Vaponephrin Company, Upper Darby, Pennsylvania.

LABORATORY RESULTS*

In all patients an attempt was made to isolate *Hemophilus pertussis* organisms. Cultures were taken daily for the first three days after admission, and in twenty-one patients they were also obtained during and after treatment. The nasopharyngeal swab method of taking cultures as described by Bradford[8] was used. Positive cultures were obtained in thirty-four of the eighty-four patients. More significantly, however, positive cultures were obtained in ten of twenty-one patients in which cultures were taken during and after therapy. In five of these patients the positive growths were from cultures taken on the third to the fifth day of treatment, and in the remaining five from cultures taken two weeks after onset of treatment.

Blood level determinations were done on samples taken three and one-half to four hours after intramuscular injection and one hour after aerosol administration. Twenty-six determinations from the intramuscular group showed an average of 46 units per milliliter of serum (one unit is equal to $\frac{1}{10}$ μg.). The range varied between 26 and 70 units with well over one-half in the 26 to 42 range. Thirteen determinations made on patients receiving aerosol therapy averaged 23 units per milliliter of serum with the range from 20 to 26 units per milliliter of serum. We noticed no significant cumulative effect, since levels taken on the first day of treatment were not appreciably different from those which were taken on the third, fourth, and fifth days. This was found to be true whether the drug was given by the intramuscular route or by aerosol. There was no correlation between the blood levels and results of treatment.

Although we used the same dosage as Brownlee and Swift, they obtained levels between 2 and 4 units per milliliter of serum. Their method of determination, however, was different from that used in our laboratory and may explain the lack of similar laboratory results. Two other laboratories,† using the same blood specimens with which we made our determinations, confirmed our results on several patients.

Sensitivity studies using Levinthal's media for the *H. pertussis* were done. Serial dilutions of Polymyxin B in saline were inoculated with the test cultures. The results showed that an average of 1.2 units of Polymyxin B were necessary to prevent the growth of *H. pertussis* organisms, a somewhat higher average than that reported by Brownlee.[6] The significant point, however, is that the blood levels with the dosage used were in all instances many times above the calculated sensitivity range.

Attempts to do the sensitivity tests by the agar cupplate method or by the direct incorporation of Polymyxin B into the Bordet-Gengou media were unsuccessful.

CLINICAL RESULTS

In Tables II and III are listed the results which were graded as improved, failure, or equivocal. A case was considered improved if there was notable im-

*Laboratory assistance was given by Arthur Vogel, B.S. Details of laboratory procedure are to be published in a separate report.

†Hobby, G. L., Chas. Pfizer and Co., Inc., Brooklyn, N. Y. Laboratory of Burroughs Wellcome and Co., Tuckahoe, N. Y.

provement in the course of the disease within seven days after the onset of treatment. Since polymyxin is a specific bactericidal agent, a discernible change in the course of the disease would be expected within this time. Improvement, as it is observed in patients successfully treated with human hyperimmune serum, occurs within a week after the onset of treatment.[9-12]

TABLE II. RESULT OF TREATMENT IN SIXTY-SIX PATIENTS RECEIVING INTRAMUSCULAR INJECTIONS ACCORDING TO AGE AND SEVERITY OF ILLNESS AT THE ONSET OF TREATMENT

AGE	CONDITION AT ONSET OF TREATMENT			RESULT OF TREATMENT		
	MILD	MODERATE	SEVERE	IMPROVED	EQUIVOCAL	FAILURE
0-6 mo.	7			3	2	2
		4				4
			8	2		6
7-12 mo.	2			1	1	
		6				6
			2			2
1-2 yr.	3			1	2	
		4		1		3
			3			3
2 yr.+	8			6	2	
		19		9		10
			0			
Totals						
Mild	20			11	7	2
Moderate		33		10	0	23
Severe			13	2	0	11
Sixty-six patients				23	7	36

TABLE III. RESULT OF TREATMENT IN EIGHTEEN PATIENTS TREATED WITH AEROSOL INHALATION ACCORDING TO AGE AND SEVERITY OF ILLNESS AT ONSET OF TREATMENT

AGE	CONDITION AT ONSET OF TREATMENT			RESULT OF TREATMENT		
	MILD	MODERATE	SEVERE	IMPROVED	EQUIVOCAL	FAILURE
0-6 mo.	2				2	
		2				2
			0			
7-12 mo.	2				2	
		4		1		3
			0			
1-2 yr.	1				1	
		0				
			0			
2 yr.	4			4		
		3				3
			0			
Totals						
Mild	9			4	5	0
Moderate		9		1	0	8
Severe			0			
Eighteen patients				5	5	8

Analysis of Table II shows that of the forty-six children who were moderately or severely ill at the onset of treatment, thirty-four failed to show improvement in seven days. It was this group for which specific therapy was needed and in which the most accurate observations as to the efficacy of the treatment could be made. The twelve children in this group who were listed as improved within seven days of the onset of therapy could not all be considered as therapeutic

responses. Six of these children were in the fourth week of illness and may simply have reflected the natural convalescence. Only two of the twelve children were under one year of age, and only two patients showed a really significant change in the course of illness. On the other hand, the thirty-six patients listed as failures showed no alteration in the course of their entire illness.

Since it might be said that the length of therapy was not sufficient to obtain a therapeutic effect, the course of therapy was repeated in two patients who had failed to respond initially. Beneficial results were not noted with the second course of treatment.

The improvement noted among the mildly ill children lost its significance in view of the lack of clear-cut criteria before and after treatment. Most were actually equivocal and may have represented natural convalescence as suggested from similar untreated patients observed during the same period of investigation. Lack of systematic controls prevented any definitive statement in this regard.

The children who received aerosol therapy (Table III) showed the same results as were observed in the patients treated by the intramuscular route. The group was small but the failures were convincing. No severely ill children were treated in this group because of the evident inability to obtain any significant results with the intramuscularly treated group.

Complications developed in fifteen patients. Nine had pulmonary involvement as evidenced by atelectasis, pneumonia, or emphysema, four had diarrhea, and two had otitis media. There were no deaths.

TOXICITY

Swift and Brownlee[5, 6] reported transient albuminuria in nine of ten patients treated with aerosporin. Laboratory studies on mice indicated the existence of a nephrotoxic factor with the main damage occurring in the tubules. Polymyxin B, the purified aerosporin used in our investigation, was thought to be free of the nephrotoxic factor. However, as shown in Table IV, albuminuria was present in thirty-three of the sixty-six patients treated with the intramuscular polymyxin. It varied from a trace to 3 plus. In most instances this was associated with few to many leucocytes per high power field (centrifuged). The albuminuria and leucocytes were transient in all patients and disappeared after treatment was concluded. Urinalyses done on twenty-one children in the follow-up clinic a month after discharge revealed no evidence of pathology. Serial nonprotein nitrogen levels taken during and after treatment in the first twenty patients showed no elevation. Single nonprotein nitrogen determinations in thirteen other patients revealed no rise above the normal.

TABLE IV. TOXICITY NOTED ACCORDING TO METHOD OF TREATMENT

TOTAL NO. PATIENTS	FEVER	URINARY FINDINGS		LETHARGY, ANOREXIA
		ALBUMIN	LEUCOCYTES	
66 intramuscular	62	33	26	60
18 aerosol	10	2	1	1

Elevation of temperature was present in sixty-two of sixty-four intramuscularly treated patients while on therapy. Elevation was coincident with the onset of therapy and persisted in most patients for as long as one day after treatment.

It was as high as 39° to 40° C. in several instances, with the average between 37° and 38.6° C. In only four children treated by intramuscular therapy did a temperature elevation fail to develop. In general, the elevation was higher in the older children.

Perhaps the most distressing toxic symptoms noted were marked lethargy, irritability, and anorexia. These were present in all but six of the intramuscularly treated patients and were severe enough in some children to necessitate the use of parenteral fluids to maintain hydration and nutrition. These symptoms were noted shortly after treatment was instituted and persisted until therapy was completed. Oliguria, which was noted in several patients, was felt to be secondary to the limited fluid intake induced by anorexia.

As might be expected with the lower blood levels in patients treated by aerosol inhalation, toxicity was less pronounced. One patient who had marked lethargy, anorexia, and irritability had a temperature of 40° C. Slight elevation of temperature was present in nine children, and in one the urine contained leucocytes.

It should be stated that other investigators, using only slightly higher dosages of polymyxin per kilogram of weight, found significant liver damage in dogs.[13] No jaundice or other clinical evidence of liver toxicity was noted in our patients, but no laboratory studies for hepatic function were done.

DISCUSSION

It is evident from the above results that no dramatic effect on the course of pertussis was noted within seven days of the onset of therapy. The question as to whether or not the duration of illness was shortened by polymyxin therapy is much more difficult to evaluate. There is hardly any therapeutic measure which has not been found by some investigator to shorten the course of pertussis. This arises from the difficulty of determining the normal course of untreated pertussis. It is generally agreed that the disease progresses in severity, reaching its peak about the second week of the paroxysmal stage and then gradually subsiding. Bamberger and Menke,[14] observing 100 untreated patients, plotted the frequency of paroxysms against the days of illness. They established a normal gradient of the decline of the frequency of paroxysms in their patients after the paroxysms had reached a peak. They felt that a therapeutic agent could best be evaluated by comparing the frequency of paroxysms, and particularly the rate of decline of paroxysms, against this norm. Fig. 1 is an illustration of the frequency of paroxysms in fifty-five of sixty-six of our patients treated intramuscularly, where treatment was started by the second or third week of illness. Patients whose treatment was instituted after that time are not included. The daily frequency of paroxysms is the median average per day and is charted against the week of illness. The gradual decline in the frequency of paroxysms as well as the number of paroxysms per day should be noted. The chart follows the pattern observed by Bamberger and Menke in their untreated patients. Other investigators using this method of analysis have found similar results in their ineffectually treated and control patients.[15-17] It is, of course, hazardous to compare one group of pertussis patients with another when all the variables are not taken into consideration. The only point which we wish to illustrate by this

graph, however, is the failure of any decided change in the occurrence of the frequency of paroxysms during the seven-day period after treatment, as noted previously, or in the declining phase of the disease. While it would be fallacious to use the comparison of one factor (frequency of paroxysms) as the one basis of evaluation, it offers a reliable index of the general over-all picture. Consideration of the other factors, such as nutrition and the general condition of the patient and the development of complications, substantiated this observation. The patients gained weight slowly, emesis persisted with the continuance of the paroxysms, and hospitalization was prolonged. As noted above, complications developed in fifteen patients.

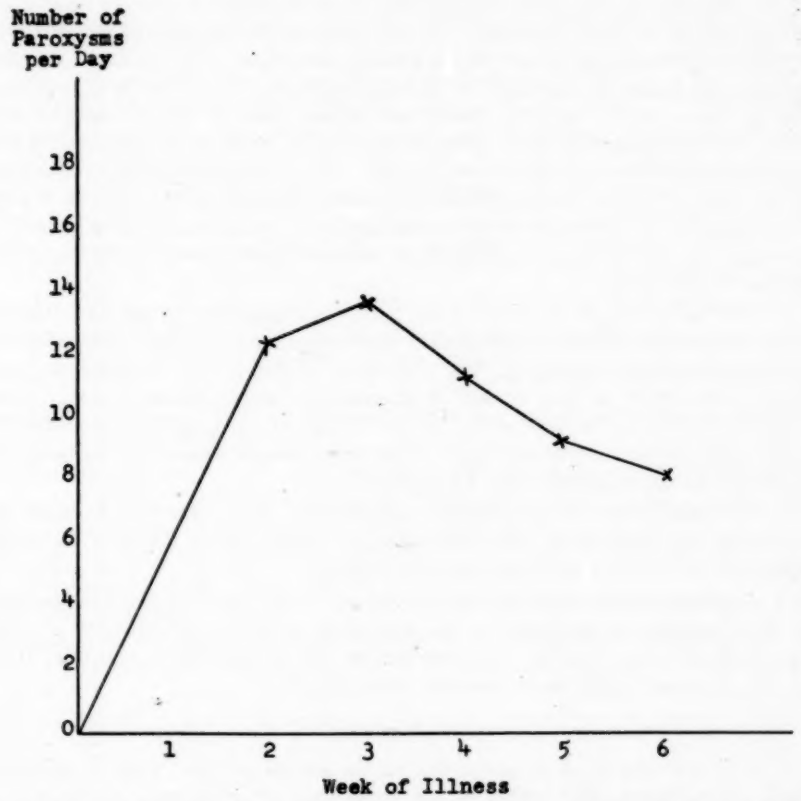

Fig. 1.—The daily frequency of paroxysms during successive weeks and illness in fifty-five patients receiving intramuscular therapy.

The roentgenologic findings were often not correlated with the clinical picture. Radiodensity of the entire right middle lobe was present without fever or malaise in one child. On the other hand, sibilant and crepitant râles with fever were often present with completely negative roentgenograms. The most significant findings were atelectasis and emphysema. This is mentioned because

the diagnosis of bronchopneumonia was frequently made prior to admission and was often not corroborated by the clinical or laboratory findings.

No deaths occurred during the period of investigation. This, however, is no reflection on the efficacy of polymyxin therapy, since the critically ill children were not included in the investigation. However, it should be mentioned that the mortality rate from pertussis has markedly decreased in recent years.[18, 19] This was evident even before the use of specific therapy and should be taken into consideration when treatment is evaluated on the basis of differences in mortality rates.

Our results, then, fail to show any significant therapeutic effect of polymyxin therapy on the course of pertussis when treatment is started during the second and third week of illness. Certainly the consistent toxic effects observed would militate against its usefulness during this stage of the disease. It is impossible for us to say whether the therapy would be more effective if instituted during the catarrhal or early paroxysmal stage. Two of the six children who were treated during this early phase of the disease went on to develop moderate and severe symptoms. These are too few patients for any conclusion to be drawn. Since there is no way of foretelling the natural progress of the disease, it must be remembered that any therapy started prior to the peak of illness cannot be evaluated by the subsequent course of the disease unless a statistically significant group is considered.

The bacteriologic findings of *H. pertussis* organisms in the nasopharynx after a course of therapy is sufficient evidence of the failure of the drug to eradicate the invading organisms. The slightly inhibiting effect of serum on polymyxin activity of in vitro studies[5] is suggestive of greater inhibition by human humoral factors. The laboratory failure to identify polymyxin biologically in urine, bile, and cerebrospinal fluid[5] is further evidence suggesting humoral and particularly tissue inactivation of the drug.

The possibility that insufficient concentration of the drug might reach the bronchial tissues through the blood stream brought about the trial of aerosol therapy. The results were no more encouraging.

Although Swift[4] concluded that aerosporin was of definite therapeutic value in the treatment of pertussis, an analysis of his results is not impressive. Only ten patients were reported, with two deaths. In view of our results with Polymyxin B, we are unable to corroborate his conclusions.

CONCLUSIONS

1. Polymyxin B, when given during the second or third week of pertussis, had no significant effect either within seven days after the onset of therapy or on the over-all disease process. There is no indication that, were treatment started during the first week, better results would have been obtained; two of six patients treated very early developed moderate to severe whooping cough.

2. Toxic effects were noted in all patients treated with intramuscular injections of Polymyxin B. Severe toxic symptoms appeared in only one patient treated by aerosol inhalation. Toxicity was manifested by fever, albumin and

cellular elements in the urine, and by lethargy, irritability, and anorexia. In all instances, the toxic symptoms and signs were transient and subsided with the discontinuance of treatment.

3. Blood levels in all determinations were many times above the sensitivity range for polymyxin on *H. pertussis* organisms obtained from patients.

4. We are unable to explain the failure to obtain favorable clinical results, despite the encouraging laboratory findings of in vitro and in vivo studies.

The authors wish to thank Dr. Donald Searle of the Burroughs Wellcome and Co., and Dr. L. Emmett Holt for their kind cooperation and suggestions during the course of this work.

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THE TREATMENT OF THE ANGINOSE TYPE OF INFECTIOUS MONONUCLEOSIS WITH GAMMA GLOBULIN

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PATIENTS with infectious mononucleosis enter the hospital with diagnoses of typhoid fever, Vincent's angina, and, most frequently, diphtheria.

Ordinarily, infectious mononucleosis requires little more than supportive care and a watchful eye by way of therapy, but it occasionally appears in severe forms and may terminate fatally.

Cases of the anginose type are characterized by severe membranous tonsillopharyngitis and it may not be possible to differentiate the membrane from that of diphtheria except by laboratory means. Generalized adenopathy and splenomegaly are usually likewise present and aid in establishing the correct diagnosis. However, the final and conclusive evidence comes from the laboratory in the form of a lymphocytosis in the differential blood count, the typical vacuolated Downey cell being present and diagnostic. The heterophile test is rarely positive before the twelfth day, so it is of little early assistance in diagnosis, but the absence of Klebs-Loeffler bacilli in the throat smears and culture is significant. Vincent's organisms are often present and may mislead the inexperienced. When the patients have first received any type of therapeutic serum, the heterophile test must be corrected by absorption.

The use of human pooled convalescent scarlet fever serum in the treatment of infectious mononucleosis was first reported by Berkley.[1] Its successful employment in our hands led us to attempt its replacement as a therapeutic agent with human gamma globulin, as we felt that the gamma globulin content of the original scarlet fever serum treatment might be the factor responsible for its beneficial result.

We use gamma globulin in doses of 4 to 8 ml. intramuscularly and one dose usually suffices. No untoward reactions have occurred.

Penicillin is also given, and occasionally sulfonamides to take care of secondary invaders, but their use alone does not favorably influence the course of the disease. Because of mistaken diagnosis or the difficulty in establishing a correct diagnosis early in the disease, 20,000 to 60,000 units of diphtheria antitoxin frequently have been given before any other therapeutic procedure. This in itself does not favorably alter the course of the disease. In this connection the disease may be startling in its resemblance to septic diphtheria: the extensive membrane and edema force the consideration of tracheotomy though careful search fails to disclose the typical vacuolated Downey cells, diphtheroids being present in smears, and no report on throat culture being available for twelve to twenty-four hours. It is because of this uncertainty in diagnosis and

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TABLE I. DIAGNOSIS, TREATMENT, AND RESULTS IN INFECTIOUS MONONUCLEOSIS

CASE NO.	AGE SEX	HETEROPHILE AGGLUTINATION TITRE	D.A.T.	PENICILLIN (DOSE, DATE)	GAMMA GLOBULIN (DOSE, DATE)	DATE OF IMPROVEMENT	NO. DAYS AFTER GLOBULIN IMPROVEMENT OCCURRED	NO. DAYS AFTER PENICILLIN IMPROVEMENT OCCURRED	MISCELLANEOUS
1	16 M	112	–	50,000 U. 4/5 q 3 h.	4 c.c. 4/8	4/10	2	5	
2	21 F	448	60,000	50,000 U. 4/8 q 3 h.	6 c.c. 4/8	4/9	1	1	
3	17 F	448	–	40,000 U. 4/5 q 2 h.	8 c.c. 4/5	4/6	1	1	
4	6 M	112	60,000	40,000 U. 1/23 q 3 h.	13 c.c. 1/23	1/26	3	3	1/23 diph. cult.
5	8 M	56	–	100,000 U. 2/14 q 3 h.	6 c.c. 2/17	2/20	3	6	
6	2½ M	56	–	20,000 U. 4/15 q 3 h.	5 c.c. 4/15	4/16	1	1	
7	7 M	224	40,000	40,000 U. 10/30 q 3 h.	8 c.c. 10/31	11/2	3	4	
8	6 F	224	–	40,000 U. 1/9 q 3 h.	10 c.c. 1/9	1/10	1	1	
9	2 M	112	–	50,000 U. 1/4 q 3 h.	8 c.c. 1/4	1/8	4	4	1/6 100 c.c. immune scarlet fever serum I.V. 1/6 Tracheotomy
10	16 F	112	40,000	60,000 U. 10/1 q 3 h.	6 c.c. 10/4	10/5	1	4	
11	14 F	224	40,000	50,000 U. 10/25 q 1 h.	8 c.c. 10/31	11/1	1	7	
12	3 F	224	–	20,000 U. 4/8 q 3 h.	8 c.c. 4/12	4/13	1	5	
13	4½ F	112	60,000	40,000 U. 3/3 q 3 h.	5 c.c. 3/4	3/6	2	3	
14	6 M	224	–	30,000 U. 3/3 q 3 h.	10 c.c. 3/3	3/4	1	1	

the known danger of withholding diphtheria antitoxin for even a few hours in such cases, should they prove to be clinical diphtheria, that antitoxin in full therapeutic dosage often is so given.

Table I shows the course of fourteen cases selected from among those treated in 1947. All were clinical cases of anginose type of infectious mononucleosis and had heterophile agglutination titers after absorption of 1:56 or higher by the Paul and Bunnell[2] method. All received gamma globulin and were the severe cases to which we have restricted this type of therapy.

CASE REPORTS

CASE 11.—A 14-year-old white girl admitted Oct. 27, 1947 had been ill six days with sore throat and fever of 101° F. On the third day of illness she was given penicillin and sulfonamides. When no response to therapy was noted and a membrane on the throat developed, she was sent to the hospital to rule out diphtheria.

Physical Findings.—Temperature was 103° F. A moderately severe pharyngitis with a dirty grey membrane on both tonsils and generalized adenopathy were present. The spleen was not palpable, but dullness was percussible to the seventh rib in the midaxillary line.

Laboratory Examination.—White blood count was 15,000; with 60 per cent lymphocytes, Downey cells being present; heterophile was 1:224 after absorption; throat culture and Wassermann were negative.

Therapy.—On Oct. 27, 1947, the day of admission, 40,000 units of diphtheria antitoxin were given, and 50,000 units penicillin every three hours; October 31, 8 ml. gamma globulin were given intramuscularly. For three days after admission temperature ran to 103° F. and membrane became worse (six days after beginning penicillin). On November 1, the temperature dropped. On November 2 the membrane disappeared. She was discharged Nov. 6, 1947.

CASE 12.—Admitted April 11, 1948, a 3-year-old white girl had been ill five days with fever of 102° F., stuffy nose, puffiness about the eyes, and sore throat. Penicillin was started two days after onset; she was sent to the hospital on the third day to rule out diphtheria because of increasing tonsillar exudate.

Physical Findings, moderately severe pharyngitis, bilateral tonsillitis with thick yellowish-grey membrane, generalized adenopathy, a palpable liver, and a questionably palpable spleen were noted. Her temperature was 102° F.

Laboratory Examination.—White blood count was 32,000; mononuclear cells were 85 per cent with many Downey cells present; hemoglobin was 13 Gm.; heterophile was 1:224. Throat culture was negative for diphtheria.

Therapy.—April 11, 1948, penicillin, 20,000 units every three hours intramuscularly, was given. On April 12 gamma globulin 8 ml. intramuscularly was administered: Temperature dropped to normal and throat exudate disappeared on April 13. The patient was discharged April 15.

CASE 9.—Admitted Jan. 14, 1948, a 2-year-old Negro boy had been ill seven days with fever and three days with sore throat, with slight respiratory distress.

Physical Findings.—Temperature was 102° F.; severe pharyngitis with yellowish exudate over both tonsils and generalized adenopathy were present; the spleen was enlarged 3 fingerbreadths to palpation.

Laboratory Examination.—White blood count was 17,500 with 68 per cent mononuclears, many being atypical; throat culture was negative for diphtheria; heterophile was 1:112 after absorption.

Course and Therapy.—On Jan. 4, 1948, 8 ml. gamma globulin and 50,000 units of penicillin were given every three hours intramuscularly; on Jan. 5, 1948, respiratory distress was increasing. Tracheotomy, at first deferred, was done on January 6 because of respiratory retraction, and 100 ml. of human immune convalescent scarlet fever serum were given intravenously. The patient was much improved on Jan. 8, 1948, and the tracheotomy tube was temporarily shut off several times. The tube was removed January 12 and the patient was discharged January 18.

It is interesting to note that Cases 4 and 13 had positive cultures for diphtheria. They were proved to be avirulent strains, however, and not causing disease. There was no question that the correct diagnosis was infectious mononucleosis.

DISCUSSION

Response to gamma globulin is shown in one or more of the following three ways: drop in temperature; disappearance or definite shrinking of the membrane or exudate; general clinical improvement, the latter being distinct from the other two and, at times, actually so dramatic that one confidently expects the patient's rapid recovery.

In this series, therapeutic response appeared within twenty-four to seventy-two hours with one exception (Case 9), and the majority of cases showed all three types of improvement simultaneously. When all three did not occur, the first response noted was the general clinical improvement with a sense of euphoria. This one we consider the most important, for it indicates that the unfavorable course of the disease has changed and recovery has started, and the temperature will drop and the throat improve in the ensuing twenty-four to forty-eight hours. These factors specifically governed selection of the date of improvement designated in the table.

Can the therapeutic response obtained in these cases have been due to the other modalities such as the diphtheria antitoxin or the penicillin? We think not. Many cases have been treated with antitoxin alone in the past, with no effect. Of this series, six received antitoxin first, and their response is no different from those that did not.

Joyce[4] has reported penicillin to be of value in the tonsillopharyngitis of infectious mononucleosis, stating that three out of four cases so treated respond with a drop in temperature within twelve to twenty-four hours. Our experience in those treated with penicillin alone generally has not shown this.

However, in this series of those receiving penicillin, five improved within twenty-four hours and seven within seventy-two hours. In contrast to this, the favorable response to gamma globulin was as follows: eight within twenty-four hours, ten within forty-eight hours, and thirteen within seventy-two hours.

By comparison, a better therapeutic response to gamma globulin is clearly indicated, penicillin showing 50 per cent improvement within seventy-two hours of administration, the severest cases showing nothing noteworthy; whereas with gamma globulin 93 per cent were improved within seventy-two hours.

The mode of action of gamma globulin remains unknown. We do not wish to minimize the effect of penicillin in these cases, but it is our belief that it acts solely upon secondary invaders while gamma globulin is turning the tide. Alone, it is rarely efficacious. Thus the combination may be better than either alone.

We believe gamma globulin should be tried in other forms of severe infectious mononucleosis, such as those with jaundice. It may also speed milder cases to recovery.

SUMMARY

1. Gamma globulin, 4 to 8 ml. intramuscularly, was used therapeutically for severe cases of infectious mononucleosis, anginose type.

2. Fourteen cases were reviewed; all had anginose type, had a heterophile agglutination of 1:56 or higher, and all received gamma globulin and penicillin.

3. Statistical evidence is in favor of gamma globulin over penicillin as the major therapeutic factor.

4. Trial on milder cases and other types of infectious mononucleosis is advocated.

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TRACHEAL TUMORS IN INFANTS AND CHILDREN

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TUMORS having their origin in the trachea are of rare occurrence in infants and children. A review of the literature fails to disclose any reference dealing exclusively with this subject. Textbooks such as *Abt's Pediatrics,*[1] *Brennemann's Practice of Pediatrics,*[2] *Holt's Diseases of Infancy and Childhood,*[3] and Mitchell-Nelson *Textbook of Pediatrics,*[4] omit mention of this condition.

We are reporting our experience with two cases along with a review of available references to such cases.

Incidence.—From the literature thirty-nine cases of tracheal tumors in infants and children were collected (exclusive of our two cases), making a total of forty-one in all. Our compilation revealed 488 instances in adults.

Pathology.—In infants and children the papillomas are most frequent (56 per cent), followed by fibromas (21.9 per cent). Angiomatous tumors were third (9.7 per cent). (Our two cases were of an angiomatous character.) There were but three cases of malignancy reported. All were of a sarcomatous nature and all occurred in infant females. This is in marked contrast with tracheal tumors in the adult. The following facts appear significant: (1) The incidence of malignancy in adults is about 40 per cent, whereas in infants it is about 7½ per cent. (2) The predominant type of malignancy in adults is carcinoma (about 30 per cent), whereas in infants and children it is sarcoma. (3) Of the benign tumors in the adult, the osteochondromas were most common (15 per cent), followed by papillomas (8 per cent) and fibromas (6 per cent). In infants the highest incidence is that of the papillomas (about 56 per cent) followed by fibromas (22 per cent). (4) Only two cases of angiomas have been reported in the adult. In infants and children it occurred in about 10 per cent.

Site.—The most frequent site of the tumor in the adult has been the lower third of the trachea, followed by the upper third; and least common is the middle third. From the meager information available it appears that the most frequent site in infants and children is the upper third, the inferior third being a poor second.

Symptomatology.—This depends on (1) site of the tumor, (2) type of attachment, and (3) size of the tumor and width of the trachea.

Position.—Tumors arising in the lower third of the trachea growing down into either bronchi gives rise to signs of partial or complete atelectasis in addition to wheezing or harsh breath sounds. If located in the upper third, interfering with the action of the vocal cords, noisy respirations and difficulty in breathing will ensue. Tumors in the middle third are less likely to give rise to severe symptoms and may go unrecognized.

From the Kingston Avenue Hospital for Contagious Diseases. Read in part before the clinicopathologic conference on Jan. 6, 1949.

Type of Attachment.—If the tumor is attached by a pedicle such as in one of our cases, it will ascend on expiration and descend on inspiration. Pedunculated tumors in the lower third, might plug a bronchus during inspiration and give rise to atelectasis, whereas on expiration they might give rise to fewer symptoms. A similar type of attachment in the upper third of the trachea may give rise to very few symptoms during inspiration but to more on expiration. If the attachment is by a broad base the symptoms will be milder, in general, as in the second case.

Size of Tumor and Width of Trachea.—Obviously, the larger the tumor the more the airway is compromised, and the more prominent the symptoms. In the wider trachea of adults one can have a fair-sized tumor with few symptoms. In a recent experience* a 76-year-old woman with a tracheal endothelioma measuring 1 by 0.5 cm., attached by a small pedicle to the posterior wall of the lower third of the trachea, had no signs or symptoms referable to the trachea. This was discovered while performing a diagnostic bronchoscopy.

Differential Diagnosis.—Tracheal tumors in infants and children giving rise to brassy cough, dyspnea, and inspiratory and expiratory difficulties, accompanied with supra- and infrasternal retractions, must be differentiated from laryngismus stridulus, cysts, and papillomas of the larynx.

In laryngismus stridulus there is a growing inspiratory difficulty starting suddenly, subsiding quickly and spontaneously, and usually occurring during the nocturnal periods. This is of a recurrent character. Laryngoscopy fails to reveal more than an excessive inpulling of the epiglottis and the aryepiglottic folds during inspiration. As the infant grows older, the attacks occur less frequently and less violently and finally subside.

Cysts of the larynx in infants and children are not uncommon and are far more common than tracheal tumors. They arise most frequently from the margins of the epiglottis and aryepiglottic folds. Hoarseness and respiratory difficulty may be present, depending on the size of the cyst and whether it is single, multiple, or pedunculated. Dyspnea is usually made worse during the act of suckling. The diagnosis is made by direct laryngoscopy. Treatment consists in the cysts' removal by use of forceps.

Papillomas of the larynx are more frequently seen than either of the two previously mentioned conditions and usually occur in females. Their most common site is on the vocal cords and less commonly on the false cords. Frequently they grow down into the trachea. (In our consideration of tracheal tumors, we have included only those that had their primary origin in the trachea and have not included papillomas which arose in the larynx and subsequently grew down into the trachea.) Characteristically, papillomas of the larynx appear in bunches, and, after repeated attempts at removal, have a tendency to recur. They tend to disappear spontaneously at about the age of puberty. This is not characteristic of papillomas of the trachea, which either remain stationary in size or start to grow in adult life, possibly becoming malignant. The symptoms of papillomas of the larynx are primarily those of hoarseness and dyspnea. Removal of laryn-

*From the Sea View Hospital Otolaryngological service of Dr. Gilbert.

geal papillomas does not result in a cure, and recurrences are constant. Tracheotomy may be necessary at times in order to give the patient sufficient airway.

Institutions maintaining a "croup service," such as that at our hospital, might have infants with tracheal tumors admitted to such a service without the tumor's presence being suspected. There are several reasons for this. From birth these children have noisy breathing. The significance of this goes unrecognized because the parents accept the noisy breathing as a normal thing and do not seek medical advice (as occurred in our two cases). However, if these children are laryngoscoped, but bronchoscopy is omitted, the cause for the noisy breathing goes undisclosed. They may then be led to believe that the infant will outgrow the noisy breathing. The child may get along fairly well until an upper respiratory infection involves the mucosa of the subglottic and tracheal area and the tumor itself. The swollen tracheal tumor now becomes an obstructive medium and gives rise to more symptoms than would ordinarily have occurred with a simple tracheitis. Suprasternal and infrasternal retractions make their appearance, associated with inspiratory difficulty. Under these circumstances the diagnosis of "croup" is readily and properly made without recognizing the presence of the tracheal tumor. Endoscopy discloses its presence. In our first case an infant child with a tracheal tumor having noisy respiration since birth developed a retropharyngeal abscess which gave rise to severe respiratory difficulty. The child was admitted in extremis with a diagnosis of "croup." Our second case with noisy breathing from birth developed an upper respiratory infection producing classical signs and symptoms of "croup."

One clinical phenomenon common to both was that attempts to gradually narrow the lumen of the tracheotomy tube in preparation for decannulation were time-consuming and extremely difficult (first case, two weeks; second case, three weeks). Furthermore, after decannulation, symptoms of noisy respiration and slight dyspnea still remained in both instances. It was not until further instrumentation disclosed the presence of the tracheal tumor and its removal that the patients were relieved of their symptoms.

CASE REPORTS

CASE 1.—E. S. On Nov. 1, 1948, an 11-month-old white male child was transferred from Kings County Hospital. He had been admitted to Kings County on Oct. 29, 1948, with a two-day history of fever and difficulty in breathing. A diagnosis of mild laryngotracheobronchitis was made there and he was placed on penicillin and sulfadiazine therapy. The child's temperature fell from 103° to 99° F. but he became markedly "croupy" and cyanotic. On admission to Kingston Avenue Hospital, he was breathing with difficulty with marked suprasternal, infrasternal, and epigastric retractions, and was very restless.

On digital examination of the pharynx and hypopharynx no obstruction was palpated. Inspection of the throat revealed moderately enlarged tonsils. Laryngoscopy revealed a markedly injected larynx, the cords moving freely. The tracheal mucosa was found to be irregularly raised and injected and in places covered with tenacious mucus. (The tumor was not recognized at this time because of the inflammatory reaction and mucus covering the tracheal wall.) The bronchi were clear. No foreign bodies were encountered.

As the child grew progressively worse, tracheotomy was performed on the date of admission.

On November 10, decannulation was attempted and because of return of obstructive signs of breathing recannulation was necessary. Decannulation was successfully accomplished on November 14.

On November 30, because of persistent slight stridor and noisy respirations, a 3.5 mm. bronchoscope was passed through a laryngoscope. The larynx was normal. At a point almost 3 cm. below the level of the cords (below the lowest end of the tracheal incision), a pedunculated, edematous mass attached to the anterior wall, moving downward on inspiration and upward on expiration, was seen. It compromised a little more than one-third of the lumen of the trachea at this site. Using a small foreign-body forceps, the tumor was removed with some difficulty. It was firm with a smooth mucosa and measured 0.3 by 0.2 by 0.2 cm. At the time of its removal it was considered to be a fibroma and it was felt that the tumor's presence explained the noisy respiration present almost from the time of birth.

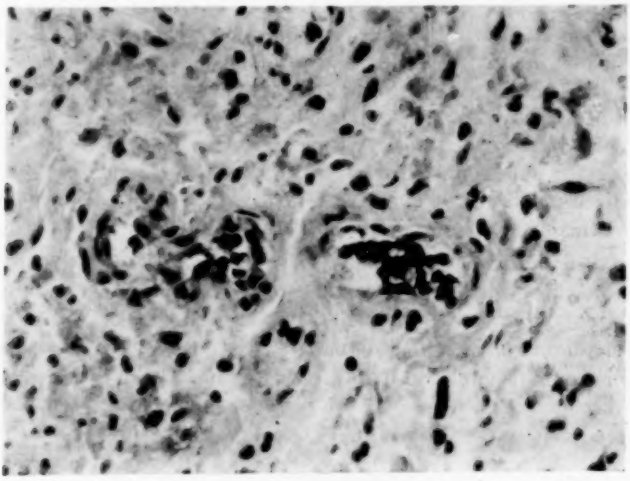

Fig. 1.—Tracheal tumor biopsy of Case 1 (hematoxylin and eosin ×450). Note the vascular spaces containing red blood cells.

The following pathologic report was made by Dr. Rosenblatt:

"*Gross.*—The specimen is a small piece of oval-shaped tissue removed from the trachea.

"*Microscopic.*—The nodule is composed of a loose stroma of fibrous connective tissue which supports numerous small channels lined by a single layer of well-preserved endothelial cells. No muscular wall can be distinguished, but in many instances there is a well-defined, broad band of pink-staining hyaline material. Some of the vascular spaces contain blood. Occasional small lymphocytes are seen within the stroma.

"*Diagnosis.*—Capillary hemangioma of the tracheal wall."

The child's condition improved, and he was discharged on Dec. 12, 1948, in good condition. A re-examination on Jan. 21, 1949, showed him to be in excellent health; he had completely lost his noisy respiration.

CASE 2.—P. L., an 11-month-old Negro female infant, was admitted to Kingston Avenue Hospital on May 28, 1946, in extremis with a history of a progressively increasing cough and dyspnea. The severity of her condition required emergency tracheotomy in the admitting room followed by intracardiac administration of adrenalin and artificial respiration. Following the tracheotomy, a golf-ball-sized mass was seen in the right side of the throat; it was incised and a quantity of foul-smelling pus was evacuated. The child's course in the hospital was febrile and stormy. Despite penicillin therapy, the abscess required incision and dilatation twice, and the child developed bronchial pneumonia. The pneumonia responded well to treatment, being aided by a transfusion of whole blood.

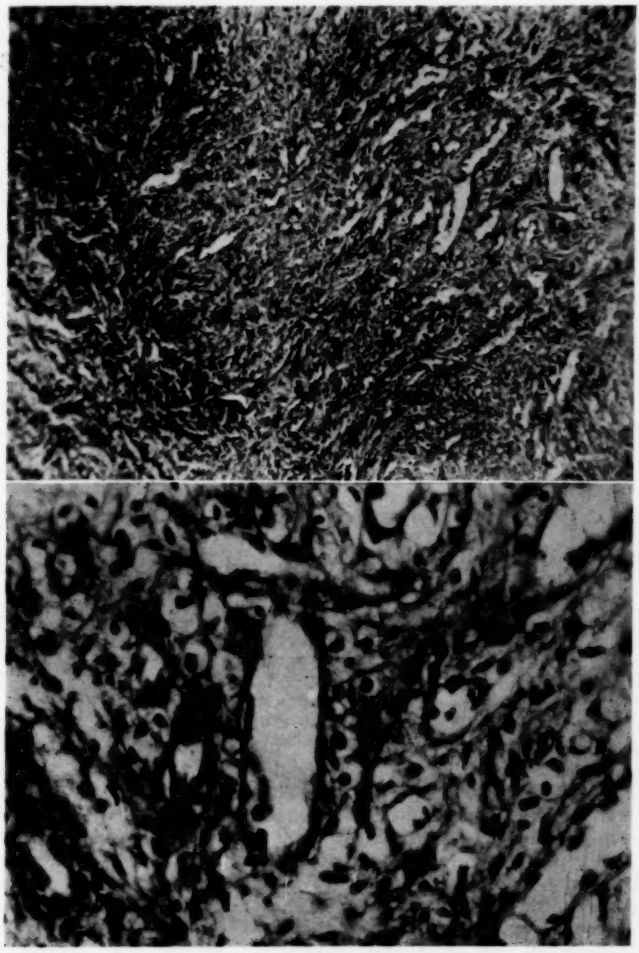

Fig. 2.—Tracheal tumor biopsy of Case 2. *A*, Hematoxylin and eosin stain, ×100. *B*, Hematoxylin and eosin stain, ×450. Note round cell infiltration with red blood cells extravasated into connective tissue stroma.

A roentgenogram of the chest showed no evidence of tuberculosis but bilateral bronchopneumonia. A roentgenogram of the cervical area showed only soft tissue swelling.

The child's condition and weight gradually improved with forced feeding and a reinforced diet. The breathing became easier. The mass in the throat subsided. The tracheotomy tube was removed on June 19 and the child remained comfortable. On July 4, the date of discharge, she was fairly well except for some noisy respirations.

On July 30, 1946, the child was readmitted with difficulty in breathing, hoarseness, stridor, and a brassy cry of one week's duration. She had been receiving diphtheria toxoid at the Department of Health station. The last injection was received on July 29. Examination showed her to be afebrile. The tracheotomy scar was well healed. She had a brassy cough, a hoarse cry, no retractions, and was breathing somewhat rapidly. The throat was red and the tonsils large. The pharynx was poorly visualized. A large amount of mucus was coughed up. The impression was that of nondiphtheritic "croup."

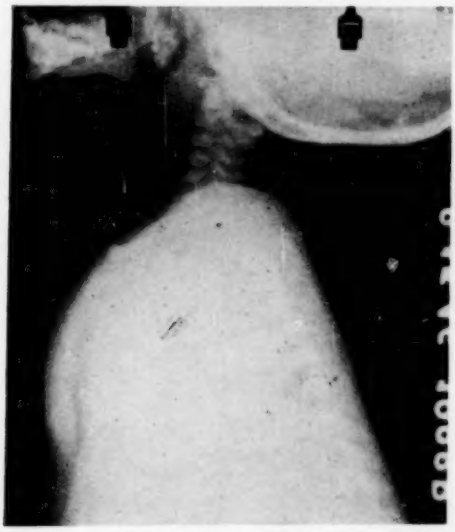

Fig. 3.—Lateral view of the neck, showing spherical density directly overlying the trachea at approximately the level of the seventh cervical vertebra. The possibility of foreign body or tumor should be considered.

Inspiratory croup continued, while epigastric intercostal retractions were becoming marked. On August 13 the child had a period of apnea following apparent regurgitation of her formula. She responded well to artificial respiration, oxygen, and suction. The child continued to have noisy respirations and some tugging and retraction of the sternum. She was put in the Trendelenberg position and given penicillin. A roentgenogram on August 15 showed the larynx and trachea to be displaced anteriorly by a retropharyngeal swelling. There was a small, round area of density in the trachea at the level of the seventh cervical vertebra.

On August 21 the child had marked retractions. A roentgenogram that day reaffirmed the presence of a small, dense mass. The possibility of a foreign body was considered. The temperature, pulse, and respiration were normal. Bronchoscopy was performed. The vocal cords appeared normal and moved freely. No obstruction in the larynx was found. In the anterior wall of trachea

at the level of the seventh cervical vertebra there was a small, flapping tumor covered by mucous membrane. Two pieces were removed and sent to the laboratory. The following pathologic report was made.

"*Gross.*—The specimen consists of two fragments of tissue. One fragment measures 0.3 × 0.2 × 0.1 cm. and is brownish-black in color. The other is gray and measures 0.6 × 0.3 × 0.2 cm.

"*Microscopic.*—One fragment is composed of loose, cellular, fibrous, connective tissue stroma, in which there are numerous endothelial-lined channels. The lining cells are occasionally swollen. The stroma is sparsely infiltrated with round cells. Attached to one surface is pink-staining fibrinous material. The other preparation is composed of dense, fibrous stroma, the fibers of which are separated from one another by extravasations of blood. The surface is denuded of lining cells, but attached to it is a fibrinous exudate similar to that described above.

"*Diagnosis.*—Fibroangiomatous polyp of the trachea.

Subsequent roentgenograms showed the absence of the dense mass previously seen. The retropharyngeal space gradually decreased to normal size. The child was discharged on Sept. 4, 1946, in good condition, with no more noisy respiration.

SUMMARY AND CONCLUSION

Two cases of primary tracheal tumors occurring in infants are reported. A survey of the literature and standard textbooks of pediatrics failed to disclose a single article dealing exclusively with this subject. A compilation of data dealing with tracheal tumors occurring in infants and children has been made, disclosing thirty-nine such cases exclusive of the authors' cases. The incidence and the types of tumors encountered is noted and compared with that of the adult. A discussion of the symptomatology and differential diagnosis is included.

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THE HOSPITAL PROGRESS OF NINE HUNDRED NINETY-TWO PREMATURE INFANTS FED EVAPORATED MILK-CARBOHYDRATE MIXTURES

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THE feeding of premature infants has assumed greater significance in recent years concomitant with the advances in our knowledge of the nutritional needs of these newborn infants. Along with this, there has been a reduction of the morbidity and the mortality and a shortening of the hospital stay. Many general principles have slowly evolved and have been more or less universally adopted for the care of the premature newborn infant, but the subject of the optimum type of feeding to be used is still controversial and a variety of milk preparations have been suggested. The belief that human milk is the only adequate food for these babies is no longer generally accepted. We are reporting a large series of premature babies, giving an analysis of the mortalities and a review of the results obtained using one type of artificial feeding, i.e., evaporated milk-Dextri-Maltose formulas.

In the four-year period between Jan. 1, 1944, and Dec. 31, 1947, there were 12,504 live births at the Beth-El Hospital. Of this group 992 of the infants were considered to be premature, approximately 7.9 per cent. This included all liveborn infants where there was any evidence of life, including heart beating or breathing. The standard for diagnosis of prematurity was any infant weighing less than 2,500 Gm. (5½ pounds) at birth regardless of the period of gestation, on the evidence that an infant of that size is not completely prepared for full, normal, independent, extrauterine life. This standard has been established by the American Academy of Pediatrics.

Analysis of the charts of these 992 infants has provided much interesting data, some of which is being presented in this initial paper. It must be emphasized at the outset that these results were obtained by an entire pediatric staff caring for a large number of babies.

A great deal has been written about the care and feeding of premature infants, but most of the papers have included relatively small series of babies. Many of the large maternity hospitals now have special provisions for the handling of their premature newborn infants. At the Beth-El Hospital a special premature nursery has been functioning since 1939. All babies weighing less than 5 pounds are sent directly and immediately from the delivery room to the premature nursery. The care of the baby in the nursery places special emphasis on individual nursing care, proper regulation of body temperature, suitable feeding, maintenance of body fluids, and prevention of infection. Although the

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great majority of these babies are private cases under the individual care of the various members of the pediatric staff, a basic regime has been set up and there is seldom any marked variation from it. These infants are taken from the delivery room in preheated blankets directly to specially constructed incubators which automatically furnish an external environment of 85° F. to 95° F. and a relative humidity of 65 per cent. Oxygen is always supplied during the first twenty-four hours and as necessary thereafter. There is a minimum of handling, but any secretions present in the upper respiratory tract are aspirated with a soft rubber catheter. It is well known that premature babies require special skills in handling; hence our nursery is staffed only by nurses who are both interested in and competent to care for these tiny infants, and emphasis is placed on their judgment.

The basic regime followed is:

A. Nothing by mouth for twelve to twenty-four hours.

B. Sterile water offered in dram quantities during the second twelve-hour period.

C. During the second day the infant is offered small but increasing quantities of an evaporated milk-Dextri-Maltose formula in the proportion of one part of evaporated milk to two parts of water with 5 per cent Dextri-Maltose. The formula is given every two to three hours and, depending upon the capacity of the infant, the quantity is gradually increased. When there is not a suitable weight gain, in the judgment of the pediatrician, the formula is gradually concentrated in proportion to the maximum of one part of evaporated milk to one part of water with 5 per cent Dextri-Maltose.

Various methods of feeding are employed. If the infant is unable to suck or swallow, he is fed by gavage. If able to swallow, but not vigorous enough to suckle, the Breck feeder or a medicine dropper is used. When the infant has vigorous sucking and swallowing reflexes, he is allowed to nurse from the bottle.

All of these infants are given vitamin K by injection during the first twenty-four hours to obviate any possibility of hypoprothrombinemia. When one week old, a suitable multivitamin preparation is given to supply the metabolic needs of the infant for vitamins A, B complex, C, and D.

Emphasis is placed on aseptic technique; masks, caps, and gowns are always worn in the nursery and all possible means of preventing infections are employed. Penicillin and the sulfonamide drugs are readily used when indicated and where active infection is suspected the infant is removed to an isolation nursery.

The fluid requirements of the infants are met by the use of hypodermoclyses, intravenous clyses, and the intravenous administration of plasma or whole compatible blood. The procedures are again subject to the discretion of the individual pediatrician.

In this paper we are presenting an analysis of the mortality rate which prevailed during the above four-year period and a statistical summarization of the progress of the surviving infants.

MORTALITY RATE IN 992 PREMATURE LIVE BIRTHS AT BETH-EL HOSPITAL

The high mortality rate among premature infants can be ascribed to several causes, all associated with their underdevelopment which, when compared to normal infants, places them at a relative disadvantage. In general, they have poorly developed cardiovascular, nervous, respiratory, and digestive systems with high frequency of intracranial hemorrhage, weak reflexes, poor maintenance of body temperature, and poorly developed or atelectatic lungs with feeble respiratory movements, reduced gastric capacity, and impaired digestive and absorptive mechanisms.

Table I presents the over-all mortality picture for the four-year period and Table II the combined mortality by weight groups. Our over-all mortality rate of 13.5 per cent compares very favorably with the 26.8 per cent of Stoesser[1] and the 27.5 mortality rate reported by Hess.[2] It is interesting to note from Table III the time of death of the one hundred thirty-four infants. Well over one-half of the deaths took place within the first twenty-four hours and approximately three-fourths during the first two days of life. It must be stated parenthetically

TABLE I. PREMATURE LIVE BIRTHS AT BETH-EL HOSPITAL FROM JAN. 1, 1944, TO DEC. 31, 1947

	1944	1945	1946	1947	TOTAL
Lived	158	182	239	279	858
Died	26	37	40	31	134
Total	184	219	279	310	992
Mortality	14.1%	16.9%	14.2%	10.0%	13.5%

TABLE II. MORTALITY RATE BY WEIGHT GROUP

BIRTH WEIGHT (GM.)	1944	1945	1946	1947	TOTAL
To 1,000					
Births	13	12	16	9	50
Deaths	13	12	15	9	49
Mortality	100%	100%	93.8%	100%	98.0%
1,001 to 2,000					
Births	50	48	73	69	240
Deaths	10	17	20	16	63
Mortality	20%	35.4%	27.4%	23.2%	26.2%
2,001 to 2,500					
Births	121	159	190	232	702
Deaths	3	8	5	6	22
Mortality	2.5%	5.1%	2.6%	2.6%	3.1%

TABLE III. TIME OF DEATH OF 134 PREMATURE BABIES

YEAR	1 MINUTE TO 1 HR.	1 HR. TO 2 HR.	2 HR. TO 12 HR.	12 HR. TO 24 HR.	24 HR. TO 48 HR.	2 DAYS TO 4 DAYS	4 DAYS TO 21 DAYS
1944	5	1	5	4	8	2	1
1945	2	2	9	9	6	3	6
1946	2	5	8	5	9	5	6
1947	1	2	7	7	5	8	1
Total	10	10	30	24	28	18	14
Per cent of total deaths	7.5%	7.5%	22.3%	17.9%	20.9%	13.4%	10.5%

at this point that in some ways ours is a selected group of infants from the point of view that all of the mothers had either been private cases of our staff obstetricians or, if service cases, had been followed in our prenatal clinic. As a consequence, most of our mothers were in relatively good health with such factors as overwork and undernourishment playing only a small role in the premature deliveries. We had no cases of congenital syphilis. All of the infants in our series were born at the Beth-El Hospital; none were delivered elsewhere and subsequently brought to the nursery.

THE PROGRESS OF THE 857 SURVIVING PREMATURE INFANTS

The second part of this paper is a summarization of the progress of the 857 surviving infants. We wish to demonstrate how a large group of babies thrived under the care of a number of pediatricians, all of whom followed the basic regime given above. The importance of this work is to demonstrate a practical approach to prematurity which can be followed by anyone who undertakes the care of these infants. The evaporated milk-Dextri-Maltose formula is easily prepared, readily available, and requires no special skills, so that the mother can easily carry on with the care of her baby upon its discharge from the hospital.

Table IV presents a complete summary of the results obtained, divided into groups according to the birth weight in grams. This method of classifying the infants will make our results comparable to those of other authors. However, all of our weighings in the nursery are in terms of pounds and ounces; hence these figures are also shown. Gordon and his co-workers[3] have found no distinction in the progress of male or females. As a consequence, we have grouped all of our cases together regardless of sex.

It will be noted from Table IV that the average day on which the birth weight was regained was 5.8 days, and that the average time for the smallest infants was 9.9 days, whereas the largest babies took only 5.1 days. When compared to the data of Hess[2] and Adams[4] as demonstrated in Table V, our results are noteworthy. In each group our infants regained their birth weight the earliest.

From Table VI it will be found that in general the hospital stays of our babies were somewhat longer than those of the above authors. However, neither one states the weight at which the babies were discharged from the nursery. We have always made it a policy to keep our babies in the premature nursery until they weigh at least 5 pounds, 8 ounces. In general, our service cases have been retained in the hospital until they attain higher weights, especially during the winter months when we prefer to send them home at 6 pounds. However, many of our babies with birth weight over 5 pounds, but under 5 pounds 8 ounces, who are not as a rule cared for in our premature nursery unless they are very feeble, are sent home before achieving 5 pounds, 8 ounces as can be seen from Table IV, because we feel that they are not as delicate as the smaller infants, and admittedly, because of the limitations of nursery space and nursing personnel. We prefer to give the tiny infants the best we can offer.

The most important criterion of any feeding regime is, of course, the weight gain of the infants on it. All of our premature infants were fed the evaporated

TABLE IV. ANALYSIS OF 857 SURVIVING PREMATURE INFANTS

BIRTH WEIGHT		NO. CASES	MALE	FEMALE	AVERAGE BIRTH WEIGHT		AVERAGE DAYS TO RETURN TO BIRTH WEIGHT	AVERAGE DAYS IN HOSPITAL	AVERAGE WEIGHT GAIN PER DAY FROM 7TH TO 28TH DAY OF LIFE		AVERAGE DISCHARGE WEIGHT		MEAN WEIGHT GAIN (GM. PER KILO)	BABIES DISCHARGED BEFORE REACHING BIRTH WEIGHT
GM.	OZ.				GM.	OZ.			GM.	OZ.	GM.	OZ.		
1,000 to 1,500	35 to 53	28	12	16	1,366.5	48.2	9.9	50.7	23.6	.83	2,537.3	89.5	15.3	0
1,501 to 2,000	54 to 70	149	69	80	1,803.0	63.6	8.3	32.2	26.1	.92	2,534.5	89.4	12.7	1
2,001 to 2,500	71 to 88	680	310	370	2,319.0	81.8	5.1	11.5	26.4	.93	2,464.9	87.3	10.9	121
Totals		857	391	466	2,197.0	77.5	5.8	16.4	26.1	.92	2,514.6	88.7	11.2	122

TABLE V. AVERAGE DAY ON WHICH BIRTH WEIGHT WAS REGAINED

BIRTH WEIGHT (GM.)	DAYS		
	BETH-EL	ADAMS	HESS
1,000 to 1,500	9.9	13.9	18.6
1,501 to 2,000	8.3	12.8	14.4
2,001 to 2,500	5.1	10.8	11.8

TABLE VI. AVERAGE LENGTH OF STAY IN HOSPITAL

BIRTH WEIGHT (GM.)	DAYS		
	BETH-EL	ADAMS	HESS
1,000 to 1,500	50.7	45.3	45.7
1,501 to 2,000	32.2	30.7	30.5
2,001 to 2,500	11.5	17.7	19.9

milk-Dextri-Maltose formulas as shown above. We have used this type of feeding because we have felt that the babies do very well on it and because it lends itself readily to preparation in large amounts in our busy formula room. The formula is easily prepared, the sterility of the milk is assured, and there is uniformity of the product.

We have never found it necessary to resort to other types of feedings to achieve satisfactory weight gains; simple manipulations of the basic formula have been sufficient. From Table IV it can be noted how well our infants thrived on this formula. From the second to fourth weeks of life it is significant that our babies averaged a daily weight gain of 0.92 ounce. When broken down by weight groups as shown, the result is gratifying.

Gordon, Levine, and McNamara,[3] in a recent report on the feeding of premature infants, have shown that "the use of mixtures of cow's milk . . . will produce larger gains in weight in premature infants than will human milk." A glance at Table VII will show that the mean weight gain per day in grams per kilogram of body weight that we obtained was comparable to that found by the above authors. We stress again that our series represents a practical approach to a large number of babies rather than an experimental program.

TABLE VII. COMPARISON OF MEAN WEIGHT GAIN FROM SEVENTH TO TWENTY-EIGHTH DAY

BIRTH WEIGHT (GM.)	MEAN WEIGHT GAIN IN GRAMS PER KILOGRAM PER DAY							
	BETH-EL		GORDON ET AL.					
	ALL EVAPORATED MILK		EVAPORATED MILK		HALF SKIMMED MILK		HUMAN MILK	
	GM.	CASES	GM.	CASES	GM.	CASES	GM.	CASES
1,000 to 1,500	15.3	28	14.9	14	17.3	31	11.7	4
1,501 to 2,000	12.7	149	13.7	25	14.2	36	12.7	12
2,001 to 2,500	10.9	680	--	--	--	--	--	--

SUMMARY

An analysis of 992 premature live births at the Beth-El Hospital is presented. These babies were all under the care of various members of the pediatric staff. All were fed and cared for according to a basic regime which is set forth in detail. The feedings were all evaporated milk-Dextri-Maltose formulas used in varying proportions.

Among the 992 premature babies there were 134 deaths, a mortality rate of 13.5 per cent. More than one-half of the deaths occurred during the first twenty-four hours and three-fourths during the first two days of life. In the group of infants weighing up to 1,000 Gm. at birth the mortality rate was 98 per cent. Where the birth weight was between 1,000 Gm. and 2,000 Gm. the mortality rate was 26.2 per cent and in the babies weighing between 2,000 Gm. and 2,500 Gm. there was a mortality rate of only 3.1 per cent.

The infants made noteworthy progress on the routine outlined. The average day on which birth weight was regained was 5.8 days with an average hospital stay of 16.4 days. Our babies made an average daily weight gain of 0.92 ounces (26.1 Gm.) during the second to fourth weeks of life and were discharged at an average weight of 88.7 ounces (2,514.6 Gm.). There was an over-all mean daily weight gain during the period from the second to fourth week of 11.2 Gm. per kilogram of body weight.

We feel that our babies have done exceptionally well on the evaporated milk-Dextri-Maltose regime outlined, and that its simplicity and uniformity, together with the excellent results herein reported, militate for its more general use in the care of premature infants.

We wish to commend the nursing staff of our nurseries without whom the excellent results reported in this paper could not have been attained.

The aid of Miss Leah Zahn and Miss Laura Shapiro, Record Librarians, was invaluable in the preparation of this report.

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MAJOR PELVIC PATHOLOGY IN CHILDREN

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MAJOR pelvic pathology in children poses a significant problem to the gynecologist and the pediatrician. Although a large number of interesting case reports have been contributed to the medical literature, negligible attention has been paid to the actual incidence of these important entities. The advantages to be gained from such a study are self-evident, especially as these are related to diagnosis and treatment.

This paper has for its purpose the review of fourteen previously unreported cases which have been observed at Charity Hospital of Louisiana, New Orleans, and to evaluate these findings in terms of practical clinical application.

ANALYSIS OF CASES

In reviewing these cases we have been impressed with the fact that one-half of the patients presented a clinical picture of an acute abdomen. The findings in the remaining children suggested chronic intra-abdominal disease, thus making available more time for detailed diagnostic study.

I. CASES OF "ACUTE ABDOMEN"

In Table I are presented the salient features of the seven cases presenting acute abdominal emergencies. Five of the children were white and two were Negro, with ages ranging from 3 to 11 years.

An analysis of the symptoms presented reveals a rather constant finding of intermittent abdominal pain varying in duration from one and one-half to fourteen days prior to hospitalization. Vomiting was a prominent symptom in five cases, but its relation to the onset of acute pain was not clear, i.e., whether it preceded or followed the first attack of acute abdominal distress. The history of purgation following the onset of acute symptoms was present in four cases, with aggravation of symptoms in two cases.

Abdominal findings were consistent in all cases in respect to distention, tenderness, and rigidity. In two cases a mass was palpable. In only two of the seven cases was there a record of rectal examination. Leucocytosis was constant, varying from 10,500 to 22,200 white blood cells per cubic millimeter.

In no case was the correct preoperative diagnosis made. Acute appendicitis and its complications, undoubtedly a more common condition, was offered as the diagnosis in six cases, and diverticulitis with abscess in one case. The immediate and pathologic diagnoses revealed torsion of dermoid cysts in two instances,

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TABLE I. CASES PRESENTING CLINICAL PICTURE OF ACUTE ABDOMEN

AGE AND RACE	HISTORY	FINDINGS	PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	OPERATION
9 yr. Negro	Dull pain two weeks. Severe pain two days with vomiting.	Distention, rigidity, tenderness in right lower quadrant. Leucocytosis.	Acute appendicitis. Possible appendiceal abscess.	Right dermoid cyst, 7 cm., with torsion of pedicle.	Salpingo-oophorectomy.
10 yr. Negro	Dull pain right lower quadrant four days, generalized one and one-half days. Pain increase in supine position, decrease in knee-chest position. Purgation.	Generalized tenderness and rigidity. Mass in lower midabdomen. Leucocytosis.	Ruptured appendix with encapsulated abscess.	Right dermoid cyst, 11 cm., with massive hemorrhage and torsion of pedicle and of tube.	Salpingo-oophorectomy.
10 yr. white	Pain and vomiting two days. Purgation.	Distention with generalized rigidity and tenderness. Leucocytosis.	Acute appendicitis with possible rupture.	Left hemorrhagic cyst, 7 cm., of ovary with torsion of pedicle.	Salpingo-oophorectomy. Closure—accidental incision of bladder. Abdomen drained.
4½ yr. white	Pain and vomiting two days. Purgation.	Tenderness and rigidity in right lower quadrant. Mass palpable. Leucocytosis.	Acute suppurative appendicitis. Possible abscess.	Right hemorrhagic cyst, 8 cm., with torsion of pedicle. Chronic appendicitis.	Salpingo-oophorectomy. Appendectomy.
3 yr. white	Recurrent pain three days with slight vomiting. Purgation.	Moderate tenderness, rigidity right lower quadrant. Distention. Leucocytosis.	Acute appendicitis, probable rupture.	Torsion of right tube with massive hemorrhagic necrosis of tube and ovary.	Salpingo-oophorectomy.
5 yr. white DEATH	Acutely ill two days. Vomiting.	Generalized abdominal tenderness and rigidity. Distention. Rectal examination—mass in pelvis. Leucocytosis.	Acute appendicitis with possible rupture and abscess formation.	Rupture of right pyosalpinx with generalized peritonitis. Acute periappendicitis.	Appendectomy. Cecostomy.
11 yr. white	Acutely ill one and one-half days. Pain in left lower quadrant. Persistent vomiting.	Tenderness in left lower quadrant. No mass palpable. No distention. Leucocytosis. Rectal examination negative.	Diverticulum of intestine with abscess.	Hemorrhagic cyst, 7 cm., of left ovary with torsion of pedicle.	Oophorectomy.

torsion of hemorrhagic cysts in three, torsion of tube and ovary in one, and ruptured pyosalpinx in one. It is interesting to note that in five of the seven cases the right adnexa were the seat of the pathology. This, perhaps, is responsible for the common preoperative diagnosis offered in six cases.

Treatment consisted of salpingo-oophorectomy in five cases, oophorectomy in one, and appendectomy and cecostomy in the remaining case.

The postoperative course was uneventful in five cases and prolonged in one case because of accidental bladder injury. The one fatality occurred six hours after operation and was due to overwhelming toxemia secondary to generalized peritonitis.

II. CASES OF "NONACUTE ABDOMEN"

Table II presents in summary form cases of the seven patients which entered the hospital with complaints of abdominal masses or symptoms of chronic abdominal pain. Of this group, five patients were white and two were negro with ages ranging from 18 months to 12 years. The three cases of ovarian malignancy occurred in a comparatively higher age group (10 to 12 years) and all these children were white.

The symptom of dull, aching, abdominal pain was the chief complaint in three cases, although an abdominal mass was also noticed prior to admission. The remaining four cases were brought into the hospital mainly because of slowly growing abdominal tumors. All three cases of ovarian malignancy gave histories of low-grade fever of several weeks' duration and in one of these there were associated nausea and vomiting.

Physical examination revealed palpable tumor masses in all cases, freely movable in six cases and apparently fixed in one instance. Rectal examination, although performed in six of the seven cases, was recorded as negative in all instances except one. Marked ascites was present in one case of malignancy necessitating aspiration before a definite mass could be palpated; pleural effusion was an interesting associated finding in this case. Additional diagnostic x-ray studies, barium enema, and pneumoperitoneum were of no apparent value except in confirming the presence of an abdominal tumor mass.

The correct diagnosis was made or suspected in six of the seven cases. Ample time for investigation and the absence of abdominal muscle spasm were contributory to the greater diagnostic accuracy in this group.

The pathologic diagnoses revealed dermoid cysts varying from 4 to 10 cm. in diameter to be present in four cases, and malignancies in the remaining three, two being sarcomas and one a papillary adenocarcinoma.

Treatment consisted of oophorectomy in three cases and salpingo-oophorectomy in one case for the benign cysts, and oophorectomy in one instance and salpingo-oophorectomy in the two cases in the malignant group. Postoperative radiation was used in the cases with malignant tumors.

The postoperative course was uneventful in all cases.

TABLE II. CASES PRESENTING ABDOMINAL MASSES OR HISTORY OF CHRONIC ABDOMINAL PAIN

AGE AND RACE	HISTORY	FINDINGS	PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	OPERATION
2 yr. Negro	Abdominal tumor.	Mass in lower left quadrant, freely movable, not tender. Rectal examination and barium enema negative.	Possible ovarian tumor.	Dermoid cyst, 5 cm., of left ovary.	Oophorectomy.
10 yr. Negro	Dull pain in abdomen two months and mass one month increasing in size. Pain relieved in supine position.	Mass freely movable, palpable 2 fingers above umbilicus. Rectal, barium enema, x-ray, negative.	Ovarian cyst vs. omental cyst.	Right dermoid cyst, 10 cm.	Oophorectomy. Appendectomy.
9 yr. Negro	Mass and dull pain in abdomen two months.	Cystic mass palpable rectally and abdominally, freely movable.	Ovarian cyst.	Right dermoid cyst, 7 cm.	Salpingo-oophorectomy.
18 months white	Mass in lower abdomen one week.	Palpable mass in umbilical area, freely movable. Aspiration of cyst—20 c.c. X-ray after pneumoperitoneum. Rectal examination, negative.	Ovarian cyst vs. mesenteric cyst.	Right dermoid cyst, 9 cm.	Oophorectomy.
12 yr. white	Painless swelling of abdomen two weeks. Slight fever.	Ascites, paracentesis—3,500 c.c. bloody fluid. Mass palpable filling entire lower abdomen, freely movable. Associated pleural effusion. X-ray of abdomen and barium enema, negative. Rectal examination, negative.	Retroperitoneal tumor.	Papillo-adenocarcinoma of right ovary, 18 × 10 × 5 cm.	Right salpingo-oophorectomy.
10 yr. white	Several attacks of dull pain in abdomen during month.	Abdomen distended. Indefinite mass palpable. No rectal examination. Low-grade fever.	Retroperitoneal tumor vs. ovarian tumor.	Round-cell sarcoma of right ovary, 12 × 14 cm.	Right oophorectomy. Resection omentum.
10 yr. white	Mass noted in abdomen three weeks. Slight fever. Occasional bouts of vomiting. No pain.	Tender, movable mass in right lower quadrant. Rectal examination, negative.	Possible ovarian tumor.	Myxosarcoma, right ovary.	Right salpingo-oophorectomy.

PATHOLOGY

Table III presents the pathologic distribution in this series.

Although the series is small, the occurrence percentages are comparable with the cases reported by Loeb and Levy.[1]

TABLE III. PATHOLOGIC DISTRIBUTION

TYPE OF PATHOLOGY	NO.	%	
A. Benign			
Dermoid cyst of ovary	6	42.95	
Hemorrhagic cyst of ovary	3	21.5	
Torsion of tube	1	7.1	
Ruptured pyosalpinx	1	7.1	
B. Malignant			
Sarcoma			
Round cell	1	7.1	21.3%
Myxosarcoma	1	7.1	
Carcinoma			
Papillary, adenocarcinoma	1	7.1	
	14	100	

INTERPRETATION

The necessity for routine rectal examination, preferably while the child is under the influence of sedation, cannot be overemphasized. It is important, however, to bear in mind that ovarian tumors may be pedunculated, and these are frequently abdominal rather than pelvic.

Although surgical management (i.e., exploratory laparotomy) of these cases is unchanged regardless of the findings on rectal examination, the attainment of an accurate preoperative diagnosis is of more than academic importance to the surgeon.

While physiologic cysts in the adult rarely require treatment or cause complications, the reverse is noted in the child where the weight is frequently the cause of torsion, not only of the pedicle but also of the adjacent tube.

Although three cases are reported as hemorrhagic cysts, it is felt that this phenomenon was secondary to torsion, which occurred in all cases, and belies the true nature of the pathology.

As estrogen can be demonstrated in the blood stream and urine of children between 8 and 10 years of age, one may assume that pituitary stimulation is present and follicle cyst formation may, therefore, be rationally explained.

DISCUSSION

The chief purpose of this study is to present a logical diagnostic routine to be employed when pelvic pathology is suspected in the prepuberal period.

The importance of a carefully obtained, detailed history is self-evident. A significant error, however, can be committed by underestimating or ignoring the history of a child and relying completely on the mother's interpretation of symptoms.

Below are listed the characteristics of the more frequently encountered symptoms applicable to pelvic pathology:

1. *Pain.*—(a) *Acute:* Acute pain, if sudden in onset, frequently indicates torsion of an ovarian cyst or rupture of a cyst with associated immediate peritoneal reaction. Both may be accompanied by symptoms of shock. Attention should be paid to circumstances preceding pain, such as falling, direct trauma to abdomen, weight-lifting, urination and defecation, all of which may be the cause of sudden torsion. At the onset pain is usually localized to the affected side but soon becomes generalized due to peritoneal reaction.

(b) *Chronic:* Chronic pain may assume the form of recurrent attacks of variable duration. Pain is usually localized to the affected side. Partial torsion of a cyst is suggested by a history of relief of pain when the patient assumes a certain posture. Chronic pain may also result from pressure on the peritoneum from ovarian tumors or from low-grade inflammatory processes.

2. *Nausea and Vomiting.*—Nausea and vomiting may be due to pain, if severe, or to sudden peritoneal irritation in cyst torsion or rupture. It may precede or occur concurrently with these conditions. The frequent occurrence of reflex vomiting in children should always be kept in mind.

3. *Fever.*—Low-grade fever is frequently associated with malignancies but usually absent in benign cysts unless these are complicated by torsion or rupture. The tendency of many children to suffer marked febrile reactions which are not commensurate with the severity of the disease makes the temperature chart difficult to evaluate. Furthermore, acute inflammatory processes frequently present little or no fever at the onset of the disease. The degree of fever cannot be regarded as pathognomonic in the differential diagnosis of pelvic pathology.

4. *Abdominal Mass.*—A notation should be made as to location when first observed, as this may indicate its point of origin. The rate of growth is also a valuable diagnostic aid.

5. *Vaginal Bleeding.*—Vaginal bleeding of any amount is important. It may indicate precocious puberty or symptoms of feminizing ovarian tumors.

EXAMINATION

General.—Inspection of the patient for the occurrence of secondary sex characteristics may make available significant information as regards granulosa cell tumors as well as pituitary and adrenal disorders.

Abdominal.—Details of technique will be omitted except to mention the general principles to be observed: (1) gain confidence of child, (2) mild sedation, especially in the nervous child, (3) extreme gentleness at all times.

The prone position for abdominal palpation may be employed, thus allowing the rebound mechanism to be better demonstrated. Attention is called to the finding that tumors of pelvic origin are most frequently abdominal in location and palpation of even mid and upper abdominal masses does not exclude or minimize the possibility of pedunculated ovarian neoplasms.

Pelvic.—Schauffler's[2] description of gross anatomical development from birth to 10 years of age offers a suitable standard of normal findings. Knowledge of these facts is prerequisite to the accurate interpretation of data secured from a properly performed pelvic examination. The cardinal points are quoted from the original text:

1. A cervix much longer in proportion to the corpus (a ratio of approximately 3:1)
2. An almost total lack of anteflexion which characterizes the adult uterus
3. A position more nearly in the axis of the birth canal
4. A relatively meager vascular and lymph supply—satisfactory only for purposes of normal nourishment.

In the immediate preadolescent period (ages 10 to 12) growth is accelerated and gross characteristics soon resemble those of the adult.

For the inexperienced examiner of children a rectal bimanual examination is preferable to a vaginal examination, even if the latter is possible. The interposition of the rectal wall facilitates in delineating the uterus and cervix as well as associated pathology. Whenever possible, vaginal examination may reveal additional important information and should not be neglected if rectal examination is indefinite.

A necessary prerequisite to either method of examination is an empty bladder.

Rectal examination will reveal the presence of a mass in many cases. By gentle use of the little finger, well lubricated, much information may be obtained. If no mass is palpable the pelvic origin of an abdominal tumor may frequently be confirmed and localized by employing the reverse bimanual examination as proposed by Rankin and Eger.[3] This consists of applying intermittent sharp pressure on the tumor in a superior direction which produces tension on the pedicle and broad ligament, readily palpable by the rectal finger. In the case of small movable tumors, repeated rectal examination is advisable and frequently necessary before palpation is possible. Fortunately the tendency of small ovarian masses to prolapse into the cul-de-sac makes eventual palpation possible.

When inflammatory conditions are suspected, induration or fluctuant masses in the cul-de-sac are usually easily palpated. Gentleness is again necessary to prevent dissemination of localized or encapsulated infection.

ADDITIONAL DIAGNOSTIC AIDS

When the clinical picture does not suggest a surgical emergency, the following additional diagnostic aids may be employed in order to arrive at the correct diagnosis:

1. *X-ray.*—The chief value of x-ray is the revelation of calcification within the mass, almost definitely labeling the tumor as a teratoma but not differentiating between the benign cyst and the malignant solid type. X-rays of the long bones to demonstrate precocious growth are also used as an adjunct to the diagnosis of feminizing tumors.

2. *Cystoscopy and Pyelograms.*—In order to rule out definitely congenital anomalies of the urinary tract and kidney tumors, these procedures may frequently be necessary.

3. *Aspiration of Cyst.*—Unfortunately this procedure is occasionally employed, despite the apparent dangers and questionable diagnostic value. It is

usually performed only in large, well-demarcated cysts lying flush to the abdominal wall in which surgery is indicated regardless of pathology. The characteristic fluid from cystic teratomas will certainly identify the tumor, but the obvious dangers in aspiration of malignant cysts preclude this procedure as a safe one.

4. *Pneumoperitoneum.*—Although advocated by some, the value of this procedure is questionable and the technical difficulty and added expense do not justify its wide use in these cases.

CONCLUSIONS

1. Major pelvic pathology is an important and not infrequent cause of symptoms referable to the abdomen in children.

2. Knowledge of the normal anatomy of the prepuberal female child is essential for the proper evaluation of pelvic findings.

3. A thorough acquaintance with pelvic pathology in the prepuberal female is essential in making the diagnosis clinically as well as at the operating table and in performing the indicated conservative or surgical treatment.

4. The child with abdominal pain is frequently first seen by the pediatrician and general surgeon. The greater relative incidence of acute appendicitis usually determines the course of treatment. More frequent consultation with the gynecologist is recommended in cases involving female children. This is especially applicable to atypical cases of acute abdomen as well as cases presenting abdominal symptoms of relatively long duration.

5. An outline for routine examination of the prepuberal female is presented.

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Case Reports

TYPHOID FEVER TREATED WITH CHLOROMYCETIN

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CHLOROMYCETIN has recently been reported efficacious in the treatment of typhoid fever by Woodward, Smadel, and collaborators,[1] and this case is presented as a contribution to the clinical literature on the subject. The drug has shown no toxic effects in previous usage with scrub typhus and endemic typhus. It is rapidly absorbed from the intestinal tract and either rapidly excreted or inactivated. These investigators treated ten typhoid patients by the tenth day of the illness, noted marked improvement in the clinical picture within twenty-four hours, and achieved a permanent normal temperature within three and a half days, on the average, from the start of the treatment. None of their patients died; two relapsed and were promptly cured by readministering the drug. It is of interest that the organisms isolated from the relapsed cases showed no increased resistance to the drug. Of their control patients, one died and the remaining seven ran an average course of thirty-five days. All of their patients were adults. Their dosage schedule was 50 mg. per kilogram body weight as an initial dose followed by 0.25 Gm. every two hours until the temperature was normal, then every three to four hours for five days.

CASE REPORT

S. C., a 6½-year-old white female, was admitted to Children's Hospital, Washington, on Dec. 24, 1948, with a chief complaint of temperature to 105° F. of five days' duration and a mild hacking cough. At the onset the temperature would rise to 102° F. but over the five-day period despite sulfadiazine and later intramuscular penicillin, when the former drug was vomited, the temperature continued to climb. A slight cough developed with the onset of the illness but was not a prominent symptom. There was no history of ingestion of raw milk or contaminated water. About four weeks previously the family had motored to another city and had eaten along the way.

On admission physical examination revealed an acutely ill child, coughing occasionally, hot and flushed, and moderately dehydrated. The pharynx was slightly injected, and ears, chest, and abdomen were entirely negative. Blood pressure was 120/78. Chest x-ray was negative as was the blood culture and heterophile antibody reaction. The urine showed some acetone but was otherwise negative. The initial blood count showed 4.4 million erythrocytes, hemoglobin 12.5 Gm., leucocytes 11,600 with 68 per cent neutrophiles of which 55 were segmented, 12 stab forms and one juvenile. Lymphocytes were 27 per cent, eosinophiles 1 per cent, basophiles 1 per cent, and monocytes 3 per cent. Purified protein derivative No. 1 was negative at forty-eight and seventy-two hours. Subsequent white blood counts showed no substantial change.

Penicillin 300,000 units a day was given intramuscularly for the first three hospital days until it became apparent that it was of no benefit and was discontinued. During this first hospital week the temperature became plateau-like, never dropping below 103° F. and ranging to 105° F. Therapy was entirely supportive, consisting of intravenous administration of vitamins B and C, and

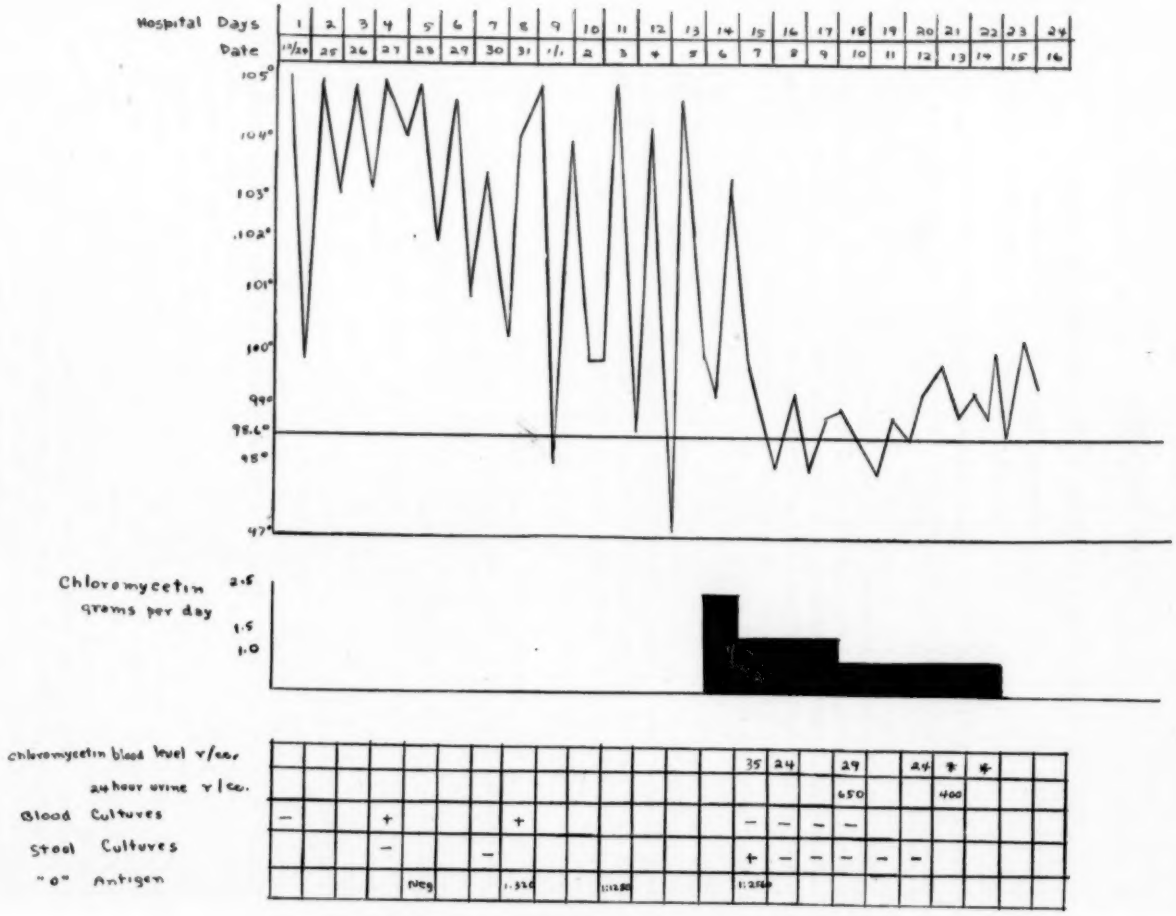
Hospital Days
Date
Chloromycetin grams per day
chloromycetin blood level γ/cc.
24 hour urine γ/cc.
Blood Cultures
Stool Cultures
"O" Antigen
* less than 10 γ/cc.

Chart I.

amino acids. A high protein, soft diet was instituted and fluids were forced. On the fifth hospital day several small pink macules that blanched on pressure were noted on the abdomen and extremities. At that time the liver extended a few fingerbreadths below the costal margin, and the abdomen was slightly distended and felt somewhat doughy on palpation. The liver continued to enlarge until at height of the illness it extended down to the level of the umbilicus. The spleen could be felt as a soft tumor on the seventh hospital day. Diagnosis of typhoid fever was confirmed that same day with a reported agglutination of O antigen in a dilution of 1:320 and H antigen in a dilution of 1:640. Similar studies done two days previously had been reported as negative. Confirmatory blood culture was reported two days later. Further laboratory data of significance are reported on Chart I. The clinical course was typical with the temperature spiking daily to 105° F. for the second hospital week. There was a steadily worsening anemia which was combated by two transfusions of 250 c.c. each of whole blood.

On Jan. 6, 1949, the nineteenth day of the illness, chloromycetin was started with an initial dose of 1 Gm. calculated on the basis of 50 mg. per kilogram of the body weight followed by 0.25 Gm. every four hours. The temperature dropped to 100° F. within sixteen hours and from then on stayed below 100° F. After forty-eight hours of normal temperature the dose was decreased to 0.25 Gm. every six hours and continued for five more days. There was one positive stool culture for *Eberthella typhosa* noted on the day following initiation of treatment and none after that. During the week of normal temperature the patient's general condition improved markedly and the liver and spleen steadily receded in size. She was discharged home on her twenty-fourth hospital day after nine days of normal temperature, twenty-eight days after the onset of the disease. Follow-up at home showed an uneventful convalescence. Subsequent stool cultures have remained negative.

COMMENT

The pertinent observation may be made concerning this case that since the drug was not started until the nineteenth day of the illness the defervescence is not conclusive. However, the rather sudden response within twelve hours, when the febrile curve had given no evidence of beginning lysis, the fact that in typhoid fever the resolution is usually by lysis over a three- to five-day period, coupled with the rather dramatic results reported by Woodward, leads me to feel that the course of this illness was shortened at least by a few days and that the subsequent negative stools, a positive one having been reported the day that therapy was begun, can be credited to the action of this antibiotic.

Facilities were available for determining chloromycetin levels in the blood and urine. The blood specimens were drawn three hours and five hours, respectively, after the drug was given, depending on whether the patient was on a four- or six-hour dosage schedule. They therefore represent the low point of blood concentration on these two dosage routines. Insofar as *E. typhosa* is inhibited in vitro by a concentration of 0.25 gamma per cubic centimeter, it can be seen that these reported levels are well above the theoretical minimum and it probably will be unnecessary in the future to follow cases with routine blood concentration determinations.

The author wishes to thank Miss Sarah Stevens for her technical assistance in determining the chloromycetin levels.

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NEPHROCALCINOSIS AND PSEUDOMONAS AERUGINOSA PYELONEPHRITIS: TREATMENT WITH p-AMINOMETHYLBENZENE-SULFONAMIDE (SULFAMYLON)

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THE purpose of this report is to describe a case of nephrocalcinosis with pyelonephritis due to infection with *Pseudomonas aeruginosa* and the results of treatment with Sulfamylon.*

The properties of Sulfamylon which are of interest have been described previously.[1-8] It is much more soluble than other sulfonamides, is not opposed in its action by p-aminobenzoic acid, and, although its range of antibacterial action is similar to that of other sulfonamides, other organisms such as the Clostridia are susceptible to its action. As will be seen later, some strains of *Ps. aeruginosa* are particularly sensitive to sulfamylon.

R. B., a 14-year-old white girl, was referred to Dr. Alexis F. Hartmann in October, 1946, because of the persistence of a urinary tract infection which had not yielded to treatment with penicillin, sulfonamide drugs, or mandelic acid. Studies of the urinary tract had revealed the presence of numerous areas of calcification throughout the kidney substance. The present illness is believed to have begun at the age of 7 years with a rather severe febrile illness accompanied by nausea, vomiting, and cramping abdominal pain. Thereafter similar but less severe attacks lasting two to three days had recurred at yearly intervals but had recently increased in both frequency and duration. During these times the urine was cloudy, and on occasion gross blood had been observed. Although sulfonamide drugs and mandelic acid had been of temporary benefit on several occasions, each soon became ineffectual. During the preceding year the patient had lost appetite and weight due to her frequent illnesses.

The patient was admitted to the Children's Hospital for study on Oct. 25, 1946, shortly after an unusually severe attack of her illness. Physical examination revealed a thin, pale, white girl who appeared to be chronically ill. There was bilateral tenderness to palpation in both flanks, but the remainder of the examination, including funduscopic, was negative. Blood pressure was 128 systolic over 80 diastolic. Chemical examination of the blood revealed serum calcium 12.7 mg., phosphorus 3.7 mg., nonprotein nitrogen 38 mg. per 100 ml., respectively. An Addis-Shevky test revealed a volume of 845 ml. of acid urine with a specific gravity of 1.009, red blood cells 66,000,000, white blood cells 150,000,000. There was a trace of albumin. Maximum urea clearance was 140 per cent of normal. A catheterized specimen of urine was cultured and revealed *Escherichia coli* sensitive to 0.1 unit per milliliter of streptomycin. Intravenous pyelogram revealed no abnormalities of the pelves or calices, but scout films revealed numerous areas of calcification throughout both kidneys (Fig. 1). In an effort to rule out hyperparathyroidism, other areas of calcification in the lungs, stomach, and choroid plexus were searched for but not found. Areas of decalcification of other bones of the body were not seen. Two twenty-four hour

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*Sulfamylon is the trade name of the product made by Winthrop-Stearns Inc., who kindly supplied the material used in this study. For convenience, the name Sulfamylon will be used throughout this paper in place of p-aminomethylbenzenesulfonamide.

specimens of urine were collected and analyzed, one containing 206, the other 233 mg. of calcium. This was considered to be within normal limits. The basal metabolic rate ranged from minus 3 to plus 8 per cent on the basis of the Wetzel Grid.

Treatment with streptomycin was begun, and after five days the urine was again cultured, revealing *E. coli* sensitive to 2 units per milliliter of streptomycin. The patient was discharged from the hospital on Nov. 8, 1946, taking Sulfamerazine 0.05 Gm. per kilogram per day. At home the patient continued to have afternoon fever, headache, backache, and poor appetite.

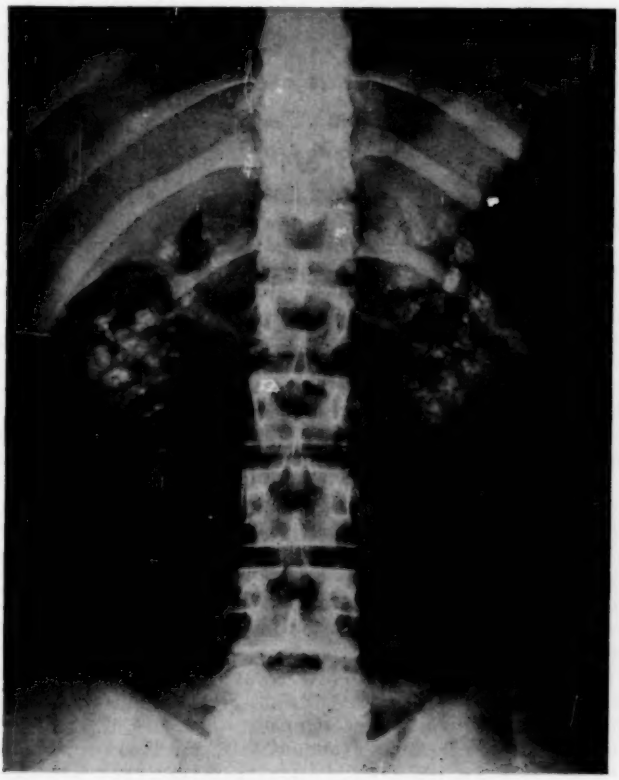

Fig. 1.—Film of abdomen showing renal calcification.

On Dec. 2, 1946, Sulfamerazine was discontinued because of the development of leucopenia, and mandelic acid was substituted. However, on Dec. 4, 1946, because of increasing fever and flank pain, she was again admitted to the hospital where she was found to have a temperature of 41° C. and mild acidosis. Chemical examination of the blood revealed a serum carbon-dioxide content of 47.0 volumes per cent, calcium 11.5 mg., phosphorus 3.0 mg., and nonprotein nitrogen 47.0 mg. per 100 ml., respectivelv. Urine culture revealed *E. coli* and *Alkaligenes fecalis*. Treatment with streptomycin was begun, and over the next five days the temperature gradually fell to normal and the urine was found to

be sterile. She was discharged from the hospital on Dec. 14, 1946, taking mandelic acid. During the next seven days her temperature gradually increased; her urine was noted to be cloudy and had a slightly greenish color. Culture revealed *Ps. aeruginosa*. On Dec. 19, 1946, there was a chill followed by a temperature of 40° C., and she was again admitted to the hospital. At this time she was acutely ill, dehydrated, and listless, with a temperature of 40° C. Blood pressure was 135/100. Chemical examination of the blood revealed serum carbon-dioxide content of 53 volumes per cent, nonprotein nitrogen 66 mg., calcium 10.2 mg., phosphorus 3.6 mg. per 100 ml. The urine was loaded with pus cells and had a greenish tint. Dehydration was corrected with parenteral fluids, and streptomycin was again administered. Over the next four days her fever persisted, and the nonprotein nitrogen gradually rose. At this time the results of the initial urine culture revealed *Ps. aeruginosa* sensitive to 10 mg. per cent of Sulfamylon. Because of the possibility that the *Ps. aeruginosa* was masking other organisms, streptomycin was continued, and Sulfamylon in doses of 2 Gm. every four hours by mouth was begun. During the following three days her temperature returned to normal but she became more lethargic and developed deep, rapid, pauseless, respiration. At that time her serum carbon-dioxide content was 17.5 volumes per cent with a pH of 7.0, sodium chloride 664 mg., and nonprotein nitrogen 83 mg. per 100 ml. In addition, phosphorus had risen to 6.4 mg. per 100 ml. Her temperature spiked to 40° C. At 9:40 A.M. on Dec. 30, 1946, she was given 30 ml. per kilogram of ⅙ molar sodium-r-lactate intravenously and a mixture containing 30 ml. per kilogram of ⅙ molar sodium-r-lactate and 40 ml. per kilogram of hypotonic Ringer's solution subcutaneously. This mixture is known as "half fortified" lactate Ringer's. Six hours later at 3:40 P.M. her serum carbon-dioxide content was 49 volumes per cent with a pH of 7.4, and she was again alert and cooperative. The next morning the serum nonprotein nitrogen was 53 mg. per 100 ml., but the carbon-dioxide content had fallen to 37 volumes per cent. Oral molar sodium lactate in doses of 100 c.c. per day was started in an effort to prevent the development of acidosis. On Jan. 9, 1947, Sulfamylon was discontinued, and culture of the urine again revealed *Ps. aeruginosa* still sensitive to 10 mg. per 100 ml. Sulfamylon. The drug was continued, and on Jan. 23, 1947, after being afebrile for five days, she was discharged from the hospital taking Sulfamylon one gram every four hours and molar lactate 100 c.c. per day.

At home she experienced some nausea after taking Sulfamylon but remained fairly well until on Feb. 7, 1947, the Sulfamylon was discontinued because of increasing nausea.

Five days later she had a chill with fever to 39° C. and the next morning had nausea, flank pain, and fever. On Feb. 14, 1947, she was admitted to the hospital for the fourth time with a temperature of 40° C., appearing acutely ill but not dehydrated. Chemical examination of the blood revealed nonprotein nitrogen 42 mg., calcium 12.9 mg., phosphorus 4.1 mg. per 100 ml. Urine culture revealed *Ps. aeruginosa* sensitive to 10 mg. per cent Sulfamylon. Treatment with Sulfamylon, 1.5 Gm. every four hours, was begun, and five days later her temperature was normal. Her maximum urea clearance at this time was 30 per cent. She was discharged on March 1, 1947, receiving 6 Gm. of Sulfamylon a day. At home she continued to be fairly well, occasional spikes in temperature being controlled with increased doses of Sulfamylon up to 12 Gm. per day. During the next three months the patient gained weight, felt better, and became more active, but continued to have fever occasionally and complained of nausea after taking Sulfamylon. Although there were occasional spikes of temperature accompanied by some flank pain, the dose of Sulfamylon was gradually decreased as she improved until on June 14, 1947, she was taking

4 Gm. per day. During this period of time there was no evidence of leucopenia or anemia. However, on June 17, 1947, she developed chills and temperature to 38.6° C. accompanied by flank pain. Sulfamylon was increased to 12 Gm. daily, but by June 19, when no improvement had occurred, she was admitted to the hospital where *E. coli* was cultured from the urine. This organism was subsequently found to be sensitive to 10 mg. per 100 ml. of sulfadiazine, Sulfamerazine, Sulfapyrazine, sulfathiazole, and sulfanilamide and to 0.5 unit per ml. of streptomycin. In the meantime Sulfamylon was administered in doses of 10 Gm. per day. Bilateral retrograde pyelograms were obtained, following which the catheters were left in place to provide for continuous irrigation of streptomycin solution. A repeat urine culture later showed both *E. coli* and *Ps. aeruginosa*. The patient was discharged on June 26, receiving Sulfamerazine 0.05 Gm. per kilogram per day and Sulfamylon 6 Gm. per day. The last urine culture had shown only *Ps. aeruginosa*. Calcium excretion studies were repeated, and on three successive days twenty-four-hour urine specimens were analyzed, showing a daily calcium excretion of between 320 and 335 mg. per day, when she was on a calcium intake of 1 Gm. (20 Gm. per kilogram) which was at the upper limits of normal according to Knapp.[9]

At home she continued to take Sulfamylon, but because of intolerance to Sulfamerazine she was given sulfathiazole. She was afebrile until August 9, when Sulfamylon was stopped, following which there was a spike in temperature which was not readily controlled with either Sulfamylon or sulfathiazole. However, in contrast to her previous episode, she felt well, and hospitalization was delayed until August 25, when she was admitted with fever, flank pain, slight dehydration, and rapid, deep respirations. Chemical examination of the blood revealed a nonprotein nitrogen of 76 mg., carbon-dioxide 27.7 volumes, Calcium 10.1 mg., phosphorus 3.7 mg. per 100 ml. Sulfamylon was given in doses of 12 Gm. per day. Parenteral fluids were given as before to correct the acidosis. After three days the temperature had become normal, and on Sept. 1, 1947, a urine culture showed *Ps. aeruginosa*. She was discharged taking 10 Gm. Sulfamylon per day.

At home until Nov. 24, 1947, she continued to take Sulfamylon in doses ranging from 6 to 12 Gm. per day. On repeated visits to the clinic her nonprotein nitrogen was between 45 and 50 mg. per 100 ml. She gained weight, felt much better, and again resumed much activity. Rare spikes in temperature were controlled with increased doses of Sulfamylon. On Nov. 24, 1947, culture of a catheterized urine specimen was reported to be sterile. However, for the most part repeated urine cultures always showed a few colonies of *Ps. aeruginosa*. It is of interest that during this first year that she had received Sulfamylon the sensitivity of the organism increased only from 10 mg. per cent to 30 mg. per cent.

On March 27, 1948, she felt well enough to go back to school but became very depressed over her illness and was allowed to drop out. She continued occasionally to have low-grade fever and on May 8, 1948, for the first time experienced renal colic and passed a few small stones. Following this she continued to be fairly well but on Aug. 28, 1948, again had colic and passed more stones, analysis of which showed them to be composed of calcium phosphate and oxalate in about equal amounts.

On Oct. 1, 1948, she started school.

Since the last period of hospitalization there has been little change in the laboratory findings. The urine has consistently been of low specific gravity, containing a trace to one plus protein and numerous pus cells. Cultures reveal *Ps. aeruginosa*. The serum nonprotein nitrogen varies between 40 and 60 mg. per 100 ml. and the calcium and phosphorus have been within normal limits.

Clinically, she has shown rather steady improvement as regards her sense of well-being, especially since being allowed to resume more normal activity. One comforting observation is that her blood pressure has remained within normal limits during this period.

At this writing she has been taking Sulfamylon for almost two years in doses ranging from 6 to 12 Gm. per day along with molar sodium lactate in doses depending on repeated determinations of serum carbon-dioxide content. There have been no toxic reactions other than occasional nausea. On Sept. 1, 1948, the *Ps. aeruginosa* was sensitive to 20 mg. per 100 ml., and on Nov. 11, 1948, showed no growth even in 10 mg. per 100 ml. of Sulfamylon.

DISCUSSION

Obviously this patient has not been cured by Sulfamylon. Undoubtedly there are obstructive phenomena, small abscesses, and much tissue necrosis surrounding the areas of calcification, providing a fertile field for bacterial growth and little chance for free drainage. That the prognosis is ultimately poor is evident. However, we feel that the use of Sulfamylon has prevented rapid progression of the disease and has prolonged the life of the patient.

The character of the renal disease is vague. The urine is of low specific gravity; albuminuria is not prominent, and there is no hypertension in the absence of acute infectious episodes. Nitrogen and phosphate retention are not present to an excessive degree. Therefore, one would be inclined to believe that the lesion is predominantly tubular in location.

Several interesting features of this case bear attention:

1. The failure of any one agent other than Sulfamylon to control the *Ps. aeruginosa* infection as is well-demonstrated by the repeated acute episodes following withdrawal of the drug.

2. The absence of anemia, leucopenia, skin rash or other toxic manifestation and the failure of the organism to develop appreciable resistance to the therapeutic agent even after a period of two years of treatment. That Sulfamylon does produce some nausea when taken by mouth became evident early in her course, and, although every effort was made to substitute another more palatable drug, it was realized both by us and by the patient that only Sulfamylon offered the relief which she sought.

3. The episode of severe acidosis on Dec. 29, 1946, occurred during a period in which the urea clearance was supernormal. This is usually interpreted as reflecting tubular damage. Since that time a patient with hydronephrosis and presumably tubular damage has been treated with Sulfamylon and became markedly acidotic within two days. After correction of the acidosis he was placed on oral molar sodium lactate and has since remained free of acidosis. These observations led to an investigation of the effects of Sulfamylon on the formation of urine.[10] The ingestion of this drug is followed within a few hours by the excretion of markedly alkaline urine, the pH of which often approaches that of blood. This base loss persists for only a short time in normal individuals and is prevented by the previous administration of ammonium chloride. These findings are similar to those of Hartmann and associates[11] in their study of the effects of sulfanilamide on acid-base balance. Apparently the normal individual is able to recover from the effects of Sulfamylon on the renal tubules in a few hours. However, the fact that two patients with tubular damage were precipitated into acidosis by the administration of Sulfamylon would seem to indicate that in the face of diminished tubular reserve one should give extra alkali.

SUMMARY

A case of nephrocalcinosis complicated by persistent *Ps. aeruginosa* infection is presented and the results of treatment with Sulfamylon discussed. That

Sulfamylon has been effective seems to be evident by the repeated episodes of severe illness following withdrawal of this drug. During a period of two years in which Sulfamylon has been given in doses ranging from 6 to 12 Gm. per day, no appreciable toxic reactions have been observed, and the infecting organism has shown little tendency to develop resistance to this agent. Sulfamylon may cause severe acidosis due to base loss in the urine, especially in the presence of renal tubular damage, and should be administered along with sufficient alkali to prevent this complication. For this purpose we have routinely employed a one molar solution of sodium lactate in doses ranging from 3 to 5 ml. per kilogram body weight per day, depending on the serum carbon-dioxide content.

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REPORT OF A CASE OF POSTVACCINAL ENCEPHALITIS IN A FOUR-MONTH-OLD CHILD WITH RECOVERY

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THE purpose of this paper is to report a case of postvaccinal encephalitis in infancy and to review the literature. The authors feel that such a report is of interest inasmuch as this clinical entity is exceedingly rare under one year of age.

To our knowledge this is the first case of a patient under 6 months of age which has been reported in the American literature. Numerous reports of cases in children over the age of one year can be found in American, British, and Continental literature.[1-19, 36, 37, 41] Flexner[20] in 1929 stated that the disease was unknown in this country in children under the age of 6 months; and our review has failed to disclose any additional American cases.

In the foreign journals, however, mention is made of this complication occurring in infants under six months of age. Sakoschansky[21] refers to the work Hewlett did in 1933 in which that author states that young infants are almost totally immune. Further, he reports a case in a child 14 weeks of age occurring ten days after primary vaccination, mild in character, with recovery. Scott[22] in 1932 in his review of British and Continental literature reports twenty-two cases over a five-year period occurring in infants under one year of age. These were collected from British, German, Polish, French, Dutch, and Scandanavian sources; but the data are largely incomplete and inconclusive with regard to diagnostic findings. Thompson[23] states that in England 63 per cent of all vaccinations were done on infants under one year of age. In that age group nine cases of postvaccinal encephalitis occurred. In those vaccinated over one year of age, or 37 per cent, eighty-four cases developed. In Holland he notes that in children under 2 years of age there is an incidence of one case in 13,531 vaccinations (0.002 per cent), while in the 3- to 12-year age group there is an incidence of one case in 3,555 (0.03 per cent).

In American reports, Armstrong[24] in 1931 and Hempelman[25] in 1936 concurred with the low incidence in infancy.

CASE REPORT

This 4-month-old white male infant was admitted to the Station Hospital on Jan. 31, 1948, with a chief complaint of listlessness of twenty-four hours' duration.

Past History.—The child was normal and full-term, delivered spontaneously as a vertex presentation without instrumentation, after a normal pregnancy. Growth and development were normal. Previous status was unremarkable with no history of contagion. The infant was breast-fed until the age of 3 months, at which time the mother placed him on a formula consisting of evaporated milk, water, and Karo syrup, on which he did well. Immunization for diphtheria-pertussis-tetanus was started (using the alum-precipitated combined preparation of Sharpe and Dohme) at the age of 2½ months. The

full course was completed on January 19 at 3½ months, when vaccination on the left deltoid by the multiple pressure method was performed. Primary reaction developed thereafter with erythema, vesiculation, crusting, and regional adenopathy.

Present Illness.—One week prior to admission (five days after vaccination) the child developed diarrhea characterized by the passage of ten to twelve greenish-yellow, watery stools unassociated with pyrexia or evidence of dehydration. Treatment was symptomatic and the diarrhea subsided after thirty-six hours.

For three days prior to admission (starting nine days after vaccination) the mother noted that the child appeared sluggish, not playful as usual, and manifested occasional vomiting. This persisted until the day before admission, at which time the child became somnolent, did not cry, and would not grasp proffered objects. Later in the course of the day involuntary movements of the left side of the face, corner of the right lip, and roving movements of the eyes were noted. This was associated with "failure to focus," inability to follow objects, and "inward turning" of the left eye. Feeding and bowel habits were normal without evidence of associated systemic reaction or pyrexia. Because of these complaints hospitalization was sought.

Physical Examination.—The child was a well-developed, well-nourished 4-month-old white male, asleep during the examination, crying only with painful stimuli. The skin was clear except for a mild ammoniacal dermatitis of the groins. The anterior fontanel admitted one finger and was under normal tension. Examination of the eyes revealed the pupils to be round, regular, and equal, reacting to light. Objective following of light was absent. Irregular gyrations of the eyes occurred, and paresis of the right lateral rectus and right inferior oblique muscles was noted as manifested by internal strabismus. The ears, nose, and throat were unremarkable. The lungs were resonant and clear to auscultation. The heart was normal in size and configuration with a normal sinus rhythm at a rate of 110 per minute. The abdomen was soft without palpable organs or masses. Neurological examination revealed the neck to be supple. There was no evidence of Kernig or Brudzinski signs. Examination of the cranial nerves revealed them to be intact with the exception of the previously mentioned findings in the right VI and III nerves. The deep tendon reflexes were physiologic, the superficial reflexes active and symmetrical, and the plantar response flexor.

Course.—Lumbar puncture was performed shortly after admission. The dura was entered between L-3 and L-4, the cerebrospinal fluid was found to be under normal pressure, and 8 c.c. of clear fluid were removed. The cell count was 19, 96 per cent of which were lymphocytes and 4 per cent polymorphonuclear neutrophiles. The Pandy reaction for globulin was negative. Total protein was 20 mg. per cent, colloidal gold curve and Wassermann negative.

On admission hemoglobin was 11.6 Gm. (Sahli), red blood cells were 3.88 million, white blood cells were 11,400 with 39 per cent polymorphonuclears, 58 per cent lymphocytes and 2 per cent monocytes.

The findings as noted remained unchanged until the second hospital day (February 2) when the infant experienced the following reaction: coarse twitching of the right frontalis muscle and right upper lid, bilateral rotatory nystagmus, abduction of the right arm associated with contraction of the biceps and rhythmic "pill-rolling" movements of the fingers. The left arm was extended and pronated, and the right leg maintained in extensor spasm with dorsiflexion of the great toe. Respirations were deep and irregular at a rate of 14 to 18 per minute. The tongue was directed to the left with

coarse fibrillations over its surface. The picture changed intermittently with hyperextension of both upper extremities over the head. The total duration of this episode was forty-five minutes. Blood calcium was 9.2 mg. per cent and carbon-dioxide combining power 52 volumes per cent.

The child for the remainder of the day was afebrile and took nourishment well, though remaining listless and manifesting persistent internal strabismus of the right eye.

On the third hospital day, occasional twitching of the left arm was noted. During the morning feeding, which was poorly taken, paresis of the right upper extremity developed with failure to respond to painful stimuli. The feeding was followed by a paroxysm of coughing and regurgitation. This was rapidly succeeded by drawing up of the left side of the face, and twitching of the nose and left facial muscles. Concommitantly the right lower extremity became rigid, maintained in extensor spasm, and the fingers of the right hand tightly flexed. This was followed by slow, clonic movements of the right lower extremity and rapid, clonic movements of the right hand. The head was turned to the left and rapid, irregular, ocular gyrations were again noted. This episode lasted eight minutes, after which there was no alteration in physical findings.

During the remainder of the hospital course there was no recurrence of a similar nature. By the fifth hospital day the child was alert and active. The right upper extremity was normal in function, ocular gyrations ceased, and internal strabismus of the right eye diminished, while the child regained the ability to follow light in all directions. The child was discharged on the seventh hospital day with minimal residual right internal strabismus. In all other respects the child was normal and active. Temperature never exceeded 100° F. (R) throughout the hospital course, fluctuating between 98.4 and 98.6° F. during the last three hospital days. Therapy was entirely symptomatic.

EPIDEMIOLOGY

A review of the literature[3, 23, 24, 26, 27, 35] reveals the following pertinent facts. Postvaccinal encephalitis is a complication of primary vaccination, rather than re-vaccination,[24] and is rare in infancy.[12, 20, 21, 22, 24, 25] The type of vaccine used bears no relation to the complication.[9, 13] The method of vaccination, as well as the degree and character of the local reaction are also apparently unrelated.[39] A tendency for grouping of cases as to time and place has been noted.[9, 23] The incidence of the disease parallels the total number of vaccinations, though is not necessarily proportional.[23] The case rate of postvaccinal encephalitis is lower in the United States than in European countries.[24, 25]

PATHOLOGY

The pathologic entity has been noted to involve the entire central nervous system,[26, 38, 39] both white and gray matter, but particularly the former. The characteristic microscopic lesion is perivascular neurone demyelinization associated with areas of extra- and intra-adventitial infiltration of leucocytes and glial cells.[24, 28] The spinal fluid is sterile with a moderate pleocytosis and increased protein. No inclusion bodies have been found.[29]

In comparing this pathologic reaction with that occurring after measles and the other exanthemata, it has been noted by Greenfield[23] that there is more perivascular infiltration and more complete demyelinization in postvaccinal encephalitis. Further, Thompson[23] states that in encephalitis follow-

ing measles the gray matter is but little affected, while in postvaccinal encephalitis both gray and white matter are involved, though the predominant reaction occurs chiefly in the latter.

PATHOGENESIS

While the pathogenesis of postvaccinal encephalitis is still in doubt, four hypotheses have been postulated: (1) accidental; (2) caused by the virus itself; (3) activation of a latent neurotrophic virus already present; and (4) allergic. The weight of available experimental data indicates that the third theory is most likely.[23, 28, 30, 31, 32, 33, 40] Rivers[33] supports this view in analogy to the so-called fever blister. The most convincing evidence that the postvaccinal condition is caused by activation of some questionable virus is found in the clinically and possibly pathogenetically similar conditions occurring independently and following other exanthems.

TREATMENT

The results of therapy are inconclusive. An over-all review reveals a gross mortality of approximately 50 per cent with the remainder usually manifesting rapid and complete recovery[25, 26, 28] Symptomatic therapy, sulfonamides, and convalescent sera[34] have not dramatically altered the course of this disease.

SUMMARY

1. A case of postvaccinal encephalitis with recovery in a 4-month-old child is presented.

2. The literature from 1928 to date is reviewed and discussed.

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A CASE OF MENINGITIS DUE TO PSEUDOMONAS AERUGINOSA (BACILLUS PYOCYANEUS) AND NEISSERIA FLAVESCENS WITH RECOVERY

LIEUTENANT COLONEL RYLE A. RADKE AND CAPTAIN GUY C. CUNNINGHAM, MEDICAL CORPS, UNITED STATES ARMY

MENINGEAL infections with *Pseudomonas aeruginosa* previously reported have been, in the main, due to involvement secondary to lumbar puncture,[1, 2, 4] penetrating head wound,[3] otitis media[17-19] or have been secondary to invasion of the blood stream from a primary focus in the umbilical cord[8, 9] or abscess.[20, 21] Several cases have been reported secondary to intrathecal administration of contaminated materials.[3, 5-7] Two cases have been reported in which the meningeal involvement appeared to be the primary involvement and not the result of systemic invasion from a recognized focus. Kliewe and Koch[10] reported a case in a 3-year-old child with recovery after eighty days in which the meningeal involvement appeared to be the only recognizable focus of infection, although they suggest that the primary site of infection was stomatitis. Vaughan, Beck, and Shelton[11] have reported a second case in a 40-year-old woman who became ill with headaches and in whom the first spinal puncture revealed 1,800 cells and from whose spinal fluid the *Ps. aeruginosa* was cultivated. Blood culture was negative and no primary focus was recognized. In a review of the literature of this subject Evans (1936)[12] reports that she was able to find twenty cases of primary meningeal involvement due to *Ps. aeruginosa*, most of them following lumbar puncture or septicemia. She discovered reports of three cases of infection with this organism in association with other organisms, namely, Friedländer's bacillus, *Mycobacterium tuberculosis*, and staphylococci. In each instance, the infection was secondary to penetrating wound of the skull, otitis media, or lumbar puncture. In her estimate of the literature as recorded the mortality was 66.6 per cent. Those that did recover did so after protracted illness ranging from fifty-four to ninety days. Cairns, Duthie, and Smith[13] record three cases with fatal outcome treated with streptomycin intrathecally, combined with sulfonamide therapy in one case and sulfonamide and penicillin medication in the other two.

Merworth, Rosenberg, and Pulito[22] report a case treated with streptomycin with recovery with residual neurological involvement which was thought to be due to intrathecal streptomycin.

Sarah Branham[14, 15] reported in 1930 the isolation of *Neisseria flavescens* from a number of cases of meningitis occurring in an epidemic of about forty cases due to the meningococcus. As far as we have been able to determine, it has not been described as causing primary meningitis in association with another organism. The present case to be discussed combined the unusual feature of infection with *Ps. aeruginosa* and *N. flavescens*, both rare organisms in connection with meningitis, particulary primary meningitis with no demonstrable portal of entry into the body.

CASE REPORT

The patient was a 3-year-old, white boy in excellent state of nutrition who had been healthy and normal, until June 4, 1948, at which time his mother

From the Medical Service, Station Hospital, Fort Knox, Ky.

noted that he seemed somewhat less vigorous than usual in his play. On June 5 he refused his lunch and manifested a disinclination to play, complaining of feeling cold and finally having to be carried home. He appeared somewhat drowsy to his parents and refused his supper. His fever was 102° F. He fell asleep but cried out frequently in his sleep and vomited in the early morning of June 6. He was irritable and feverish and vomited again on awakening June 6. About 9:00 AM, June 6 he lapsed into a semistupor from which he could be aroused with difficulty and he was brought to the hospital. He had had no respiratory symptoms, no bowel disturbance other than the vomiting alluded to above, and there were no symptoms referable to the urinary tract. On admission he was irrational and cried out shrilly without external stimulus. Temperature was 101° F. His skin showed residual scars of a recent chicken pox There were no petechial hemorrhages. His spleen was barely palpable and there was a grade 1 systolic murmur at the mitral area. The eardrums were normal. Kernig's and Brudzinski's signs were present and he had a rigid neck. Lumbar puncture was done and cloudy fluid was withdrawn; 5,000 units of penicillin were injected intrathecally at this time. Smear of this fluid contained numerous gram-negative cocci and diplococci of variable size, a few gram-positive cocci and diplococci of similar morphology and numerous gram-negative bacilli. Sugar was 30 mg. per cent, Pandy 2 plus, cells 980, 95 per cent polymorphonuclear leucocytes. On admission red blood cells were 3.42 million, hemoglobin 11 Gm. white blood cells 9,950, neutrophiles 66 per cent, lymphocytes 32 per cent. A second spinal tap done that same day for the purpose of introducing streptomycin yielded a similar smear. Because of the pleomorphism of the organisms seen in the smear, it was decided to treat the patient with penicillin, 100,000 units every two hours, streptomycin .25 Gm. every three hours, and sodium sulfadiazine .75 Gm. at once intravenously and then 4 Gm. subcutaneously in three divided doses each twenty-four hours. In addition, 15,000 units of streptomycin were introduced intrathecally on the first hospital day and 25,000 units on each of the second and third hospital days. A presumptive diagnosis of influenza bacillus meningitis was entertained at this time, but the penicillin was included because of the baffling nature of the smear of the spinal fluid. Initial spinal fluid culture was reported as showing *Ps. aeruginosa*. Blood culture was negative. Chest x-ray was negative, throat culture reported as showing *Neisseria catarrhalis* as the predominating organism. Spinal fluid culture taken the second day showed growth of *N. flavescens* and *Ps. aeruginosa* and the smear was similar to the one described above. This specimen had 8,200 cells, 84 per cent polymorphonuclear leucocytes, sugar 16 mg. per cent. Cultures of spinal fluid on the third and sixth hospital days were negative. The course in the hospital was one of steady improvement. He was conscious and able to take nourishment by mouth on the second hospital day and was afebrile on the sixth hospital day. He developed minor convulsions on the third hospital day confined to the face and right arm. All medication was discontinued on the tenth hospital day. When he was discharged from the hospital on the twenty-second day, he had some minor evidences of involvement of the vestibular apparatus. When re-examined thirty days later, there was no evidence of involvement of any nerve, either motor or sensory, his gait and station were normal, and his Romberg was negative.

DISCUSSION

This case represents as nearly as can be determined simultaneous involvement of the meninges with two organisms rarely primarily invasive and without evidence of a primary focus of infection. The smear of the spinal fluid taken on admission contained both organisms and although the *N. flavescens* was not

recovered from the first specimen culturally, it was readily recovered from the specimen taken the next day and was seen in the first three. No evidence of the gastrointestinal or genitourinary tract being involved was secured and chest x-ray was negative. In retrospect the *N. catarrhalis* found in the throat culture may have been the *N. flavescens;* however, this was not proved. His prompt recovery without residuals is in sharp contrast to the previously described cases of *Ps. aeruginosa* meningitis and is probably due to the fact that his mixed infection made him critically ill in a short time, thus bringing him under treatment very early. It seems likely that the convulsive disorder seen on the third hospital day was a result of intrathecal streptomycin medication, although this cannot be stated categorically. The cases of *N. flavescens* meningitis described by Branham were similar in course to meningococcic meningitis, and the onset of this boy's illness is reminiscent of such an illness.

SUMMARY

1. A case of meningitis due to simultaneous invasion with *N. flavescens* and *Ps. aeruginosa* is presented.

2. It is thought that this represents the only reported case of primary involvement of the meninges due to *Ps. aeruginosa* in company with another organism with no injury or portal of entry through infected ear or lumbar puncture.

3. Conversely, it is believed that this is the only reported case of *N. flavescens* invading the meninges in company with another organism.

4. Prompt recovery is attributed to the fact that the fulminating character of the illness brought the patient under treatment very early in the course of the disease.

5. Streptomycin is believed to have played a vital role in the recovery of this patient.

6. Convulsions occurred which were thought to be due to intrathecal streptomycin.

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Clinical Conference

CONFERENCE AT THE CHILDREN'S MEMORIAL HOSPITAL OF CHICAGO

DR. J. A. BIGLER AND DR. STANLEY GIBSON

Case 1. Congenital Dermal Sinus

DR. LEININGER.—Chief complaint: Prolonged intermittent fever; irritability.

We are presenting the case of a 22-month-old white male infant who apparently had enjoyed good health up until the present illness, which dates back to the third week in May, 1948, when a small dimple over the lumbar area of the back began to discharge a thin, yellow material. This continued on and off until July, 4, at which time the father observed that there was no longer any discharge present. That evening the child vomited and was found to have a rectal temperature of 102° F. The next morning he developed generalized malaise and his fever persisted. He was seen by a pediatrician in Grand Rapids, Mich., and the parents were told that he had a mild infection of the throat and ears. The following day he seemed somewhat improved; however, on July 7 he was more irritable and his temperature again rose to 102° F. On the eighth day of July he was admitted to Butterworth Hospital, Grand Rapids, Mich., because of stiffness of the neck. A lumbar puncture was performed and the spinal fluid was cloudy with 1,584 cells, 90 per cent of which were polymorphonuclear leucocytes. The sugar was 35 mg. per cent. The Pandy was one plus. No growth was obtained upon culture. Urinalysis was negative. The red blood count was 4,400,000 per cubic millimeter. The differential revealed 74 per cent neutrophiles, 8 per cent lymphocytes, and 18 per cent monocytes. Penicillin 100,000 units every three hours, streptomycin 25,000 units every three hours, and adequate doses of sodium sulfadiazine were instituted. The penicillin and streptomycin were discontinued after one week of therapy. His progress while in the hospital was uneventful except for occasional spikes of fever during the first week. He was finally discharged from the hospital July 28 with a spinal fluid which showed a cell count of 62, 80 per cent of which were neutrophiles, and a sugar of 39 mg. per cent. He was asymptomatic until two days later, when he again became quite irritable and his temperature rose to 102° F. Because of continued elevation of temperature he was readmitted to the hospital on August 2, at which time spinal fluid examination revealed 1,320 cells, 40 per cent of which were neutrophiles, and a one plus Pandy. The complete blood count was essentially unchanged. He was given glucosulfadiazine, streptomycin, and penicillin. He continued to run an intermittent, febrile course but was not drowsy and only slightly irritable. There was a mild stiffness of the neck and back. On August 5 a lumbar puncture revealed 900 cells, 60 per cent of which were neutrophiles, and a one plus Pandy. X-rays of the mastoids were negative.

A tuberculin test (1:1,000 O. T.) was negative. Urinalysis was negative. Because of the persistent, low-grade, otitis media which seemed to be present, an otolaryngologist was called in concerning the advisability of a bilateral myringotomy. He did not feel that the procedure was indicated. A neurosurgeon had been consulted concerning the dimple in the skin over the lumbar area and its possible relationship to his present illness. He believed that a pilonidal sinus was present and that it had no relationship to the meningitis.

On admission the child appeared surprisingly well in view of his illness for the past month. The only positive findings upon examination were mild irritability, a slightly stiff spine, and apparently mild pain upon flexion of the neck; however, there was no actual nuchal rigidity. The Kernig and Brudzinski signs were negative. Fundoscopic examination revealed no papilledema. Both tympanic membranes appeared slightly reddened but there was no bulging, perforation, or discharge.

A lumbar puncture was performed and a cloudy fluid containing 638 cells, 90 per cent neutrophiles, was obtained. The Pandy was one plus. The protein was 37 mg. per cent, the sugar 38 mg. per cent, and the chlorides 749 mg. per cent. Anaerobic and aerobic cultures were taken. No growth was obtained on the latter but Brewer's thioglycollate media revealed a growth of gram-negative, pleomorphic bacilli showing bipolar staining. Attempts to subculture this organism were unsuccessful and a Quellung reaction was negative. Complete blood count was essentially the same as before except that there was now a milk leucocytosis (16,300 per cubic millimeter). Urinalysis was negative.

The child was placed on a general diet and specific therapy, consisting of 125,000 units of streptomycin subcutaneously every three hours, 30,000 units of penicillin every three hours, and 1.5 grains of sulfadiazine per pound of body weight per day in divided doses every four hours.

X-rays of the skull and mastoids were reported as normal. Dr. George S. Livingston examined the child and believed that the initial ear infection could have been responsible for a serous meningitis, which would explain the absence of pyogenic organisms in the cerebrospinal fluid. He doubted the presence of a brain abscess and felt that the significance of the sinus over the lumbar area should be evaluated by Dr. Douglas N. Buchanan. Dr. Buchanan reviewed the history and examined the child on August 11, at which time he observed that the sinus was present in the center of a small, flat hemangioma. He pointed out that this sinus was over the area of L_5, rather than lower down in the usual region of a pilonidal sinus. His diagnosis was congenital ectodermal sinus with probably a deep abscess, and he felt that the recurrent meningitis was unquestionably a complication of the dermal sinus. He recommended that a neurosurgeon remove the dermal sinus in its entirety after the present infection had subsided completely. Because of the nature of the illness, he prognosticated that in spite of continued adequate therapy, recovery would be quite slow.

Upon his suggestion, the therapy which had been instituted at the time of admission was continued and spinal fluid examinations were obtained at weekly intervals. On August 16 the spinal fluid contained, 1,510 cells, 94 per cent of which were neutrophiles. The previous results were once again obtained upon

attempting to culture the organism. The protein was 102 mg. per cent, sugar 24 mg. per cent, chlorides 696 mg. per cent. On August 23 another spinal tap revealed 1,020 cells, 96 per cent of which were neutrophiles. The protein was 96 mg. per cent; sugar 22 mg. per cent; and the chlorides 699 mg. per cent. No organisms were obtained upon cultures. A specimen of the original organisms cultured has been sent to the Illinois State Public Health Laboratory; however, no report has been received up to the present time.

While in the hospital the patient followed a fairly uneventful course. He was occasionally irritable but never manifested a cerebral cry or pronounced nuchal rigidity. Fundoscopic examination continued to be negative and no localizing signs attributable to a space-occupying cranial lesion were ever observed. In spite of the prolonged streptomycin therapy he had shown no evidence of eighth-nerve irritation or deafness. He had a fairly good appetite during his stay in the hospital and gained two pounds in a period of three weeks. An interesting feature of his course in the hospital was his temperature curve. In spite of fairly high doses of penicillin, streptomycin, and sulfadiazine, he continued to have an intermittent, spiking fever (up to 103° F.), usually once a day.

Dr. Buchanan was consulted August 24. The temperature curve and the most recent spinal fluid findings were described to him. He believed that the present therapy was adequate in dosage and method of administration and that continued therapy would be necessary for at least four to six weeks more. In view of the fact that there were adequate hospital facilities and professional care, including a neurosurgeon, in Grand Rapids, Mich., he recommended that the child be transferred back to Butterworth Hospital for continued care and final treatment of the present illness. Such arrangements were made with the referring pediatrician and the child was discharged Aug. 25, 1948. His further progress will be reported to us at a later date.

This is the fourth case of congenital dermal sinus which has been observed at Children's Memorial Hospital, two of the previous cases having been reported by Walker and Bucy in 1934 following surgery at Bobs Roberts Hospital. The other unreported case at this hospital is that of a child who has not yet been discharged and who is receiving treatment by the orthopedic department for multiple congenital orthopedic anomalies. She was first seen at one year of age, at which time her presenting symptoms were paresis of the left leg and paralysis of the right leg. A diagnosis of myelodysplasia (T_6—S_2) and a congenital dermal sinus at L_2 was made. Surgical excision of the sinus was recommended at a later day; however, shortly thereafter she developed an influenzal meningitis which was treated successfully with streptomycin for seven days and sulfadiazine for fourteen days. Surgical excision has been deferred since, because the advisability of such a procedure has been questioned in view of the extensive myelodysplasia. At the present time the child has paresis of the left leg, paralysis of the right leg, and fecal and urinary incontinence.

Congenital dermal sinus is a relatively rare condition, as manifested by the fact that most of the pediatric textbooks and texts on pediatric neurology devote

usually less than one-half page to a complete discussion of this medical entity. A review of the literature also reveals that only nineteen such cases have been described. Table I lists these cases, the age at which the disease was first observed, and the level at which the dermal sinus entered the vertebral column.

TABLE I*

AUTHOR	LEVEL	AGE
Clark (1918)	C4	13 years
Moise (1926)	S1	18 years
Ripley and Thompson (1928)	S2	3½ months
Sharpe and Sharpe (1928)	T11	3 years
Ottonello (1933)	T3	20 years
Hipsley (1933)	T1	3 years
Walker and Bucy No. 1 (1934)	T4	5 years
Walker and Bucy No 2 (1934)	L4	3 years
Walker and Bucy No. 3 (1934)	L5	3 years
Hamby (1936)	L3	20 years
Stammers No. 1 (1938)	S1	2 years
Stammers No. 2 (1938)	S4	4 years
Boldrey and Elvidge (1939)	L5	2½ years
Kooistra (1942)	T3	19 years
O'Connell (1942)	L4	4 years
Shenkin, Hunt and Horn (1944)	S2	2 years
Waring and Pratt-Thomas No. 1 (1945)	L5	10 years
Waring and Pratt-Thomas No. 2 (1945)	L3	16 months
Cliffton and Rydell (1947)	S2	22 years

*From Cliffton, Major E. E., and Rydell, Lt. J. R.: Congenital Dermal (Pilonidal) Sinus With Dural Connection, J. Neurosurg. 4: 280, 1947.

Walker and Bucy (1934) pointed out that although pilonidal sinus was a relatively common occurrence, the instances in which a connection with the subdural or subarachnoid space was demonstrated, either at surgery or by clinical signs of localized abscess or meningitis, were relatively uncommon. By referring to the above table it can be seen that there have been only six such cases where a sacrococcygeal sinus was present. In significant contrast to this observation is the fact that such a communication has been demonstrated in all reported cases of congenital dermal sinus of the lumbar, thoracic, or cervical areas. The most commonly encountered complication of a congenital dermal sinus has been a subdural or subarachnoid abscess with resultant neurologic findings due to pressure and adhesions (paraesthesia, paralysis, fecal and/or urinary incontinence). Meningitis has occurred in at least eight of the previously reported cases (Moise, 1926; Ripley and Thompson, 1928; Walker and Bucy, 1934; Stammers, 1938; O'Connell, 1942; Shenkin, Hunt, and Horn, 1944; Waring and Pratt-Thomas, 1945). Recurrent meningitis has been observed in several instances, and for this reason the possibility of a congenital dermal sinus should be considered in any case where a child has suffered from recurrent attacks of meningitis.

Clinically, the diagnosis of congenital dermal sinus has seldom been made prior to the onset of symptoms due to a complicating infection; however, if one is aware of this medical entity and thorough in all routine physical examinations, the diagnosis can be made in an otherwise apparently normal child. The sinus usually lies in the midline of the back and is discernible on the surface of the skin as a tiny dimple, pinpoint in size, which usually lies in the center of a

small area of pigmentation. At surgery the sinus is observed to course perpendicularly to the skin through the soft tissues as an ectodermal tube 3 to 10 mm. in diameter. Its course continues through a bony defect in the vertebral column, usually at a point cephalad to the skin dimple. A spina bifida occulta, therefore, is usually observed (only one case has been reported where a spina bifida occulta was absent, Walker and Bucy, 1934). The skin dimple can best be demonstrated by examining it through a plus 8 lens of an ophthalmoscope. The diagnosis of congenital dermal sinus can, therefore, be made upon the observation of a tiny skin dimple in the midline of the back over the lumbar, thoracic, or cervical area, with concomitant spina bifida occulta.

The origin of congenital dermal sinus and its relationship to pilonidal sinus are controversial issues. Previous investigators have suggested that sacrococcygeal sinuses, or so-called pilonidal sinuses, arise from the vestiges of the medullary canal (Herrmann and Tourneux, 1887; Mallory, 1892; Gage, 1935-36; Oehlecker, 1926; Weeder, 1933; Shenkin, Hunt and Horn, 1944; and Cliffton and Rydell, 1947). Walker and Bucy (1934) point out that such an origin is not conceivable in dermal sinus occurring in the higher segmental levels, and that some other explanation must be given. They conclude that at the time when the cutaneous-epithelial ectoderm and the neuroepithelial ectoderm should have separated (first month of intrauterine life), the cleavage between them was incomplete at the particular point where the sinus occurred; thus the neural tube carried down with it a narrow invagination of the skin, clothing it with a mesodermal covering continuous with its own connective tissue covering, the meninges. Whether this same explanation of the etiology is true for pilonidal sinus is a matter for conjecture, but it is at least a possibility (Fere, 1878; Stone, 1924; and Fox, 1935).

DR. GIBSON.—Do these cases all have meningitis?

DR. LEININGER.—Eventually, yes. The first symptoms may be due to abscess formation at the end of the sinus with pressure symptoms. Findings of a sterile or serous meningitis may be present, but eventually all patients will develop a bacterial meningitis.

DR. BIGLER.—Should a dermal sinus be removed surgically as soon as detected, even in the absence of symptoms?

DR. BUCHANAN.—Yes, because of the fact that we feel that infection eventually complicates any case of dermal sinus. Surgical removal is much simpler before this complication has arisen.

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Case 2. Infectious Hepatitis

DR. LEININGER.—Chief complaint: large abdomen; yellow skin.

This child was born Sept. 26, 1947, was admitted to the Children's Memorial Hospital on July 20, 1948, and died on July 28, 1948.

This 10-month-old female infant of Jewish extraction was apparently well until three or four weeks prior to admission, when the parents noted that her abdomen was getting progressively larger. During this time she acquired a dark yellowish tinge to the skin and was somewhat apathetic. Her urine became unusually yellow and sometimes almost greenish-yellow. She was having approximately two bowel movements a day and these were foul-smelling, light cream in color, foamy, and well-formed. She vomited on three or four occasions but this consisted only of ingested food and there was no bile or blood observed. The patient was seen by Dr. Alfred Traisman, who advised admission to the hospital for investigation.

Past history revealed a normal pregnancy and a normal full-term delivery. She weighed 6½ pounds at birth. She had been in good health except for occasional colds. Development was slightly delayed in that at 10 months she could not sit by herself and no teeth were present. She received her whooping cough immunization at 7 and 8 months of age and her diphtheria-tetanus at 9 months. There was no history of exposure to phenol, benzol, or persons ill with jaundice. The family history was essentially negative.

Physical examination upon admission revealed a well-nourished but only fairly well-developed, mildly jaundiced, female infant, in no acute distress. The only other positive findings were noted on examination of the abdomen. It was distended, but there was no evidence of a fluid wave. The liver was

down two fingerbreadths and the spleen was questionably palpable. The diagnostic impression was obstructive jaundice.

On July 22 small, round, hard, movable nodes were felt in both inguinal regions and in the axillae. The liver seemed larger and more tender. The jaundice was more pronounced. The patient went downhill gradually and on July 22 she was dyspneic and stuporous. Oxygen, intravenous fluids, and penicillin were administered. Later that day the child went into coma and had an emesis of coffee-ground material. Twitching and carpopedal spasms were noted, for which calcium gluconate and blood were administered. The respirations became even more labored and numerous ecchymotic areas were noted. The patient expired the following day. Fever was present only terminally and while in the hospital she received only one transfusion, consisting of 70 c.c. of compatible blood on July 27.

Laboratory examinations.—Laboratory examinations revealed the following:

Blood: On July 21, hemoglobin was 12.5 Gm.; red blood cells 4,300,000; white blood cells 11,400; platelets 218,000. Differential count was polymorphonuclears, segmented 23, stabs 5; lymphocytes 71; monocytes 1; reticulocytes 4.5 per cent. July 27 hemoglobin was 10.8; red blood cells 3,490,000; white blood cells 29,750; platelets 238,000. Differential was polymorphonuclears segmented 6, stabs 5; lymphocytes 19; monocytes 12, atypical lymphocytes 58. Coagulation time was 3½ minutes (normal 2 to 4). Bleeding time 2½ minutes (normal ½ to 3). Tourniquet test was negative.

Blood Wasserman and Mantoux 1-1,000 were negative.

Bone marrow biopsy done on July 26 showed that the predominant cell was an abnormal marrow constituent. "It suggests a malignancy which has invaded the bone marrow." (Dr. Pierce.)

Blood chemistry on July 23 showed an icteric index of 71 (1 to 6 normal); cholesterol 316 (150 to 230 normal); cephalin flocculation 4 plus (normal 0) and on July 26 icteric index was 108, cholesterol 308. Van den Bergh gave an immediate direct reaction and an indirect positive strong. Heterophile agglutination was 1/32.

Urinalysis on July 20 showed bile 2 plus, but otherwise was negative. Benzidine was negative. Culture showed *Escherichii coli.* Urobilinogen 1.2 mg. per 100 c.c. (normal 0 to 8 mg.).

Stool on July 20 showed urobilinogen 1 plus (normal 1 to 3 plus); unchanged bilirubin 0 (normal 0); benzidine negative.

Radiologic report July 20 showed that flat plate of the abdomen was negative. On July 21, the chest was negative but the abdomen suggested the presence of fluid. On July 23 an intravenous pyelogram was negative.

DR. PEDVIS.—The major problem in this case was to discover the etiology of the jaundice. Hence we will begin this discussion by reviewing some of the more recent information on this subject.

Jaundice may be defined as a discoloration of the body tissues and fluids by bile pigment. The liver cells help to form bile which is made up of bile salts, bile pigment, cholesterol, mucin, mineral salts, lipid fractions, and urea. We are primarily interested in the bile pigment-bilirubin which is the cause of jaundice. Bilirubin is derived from hemoglobin. Hemoglobin is made up of 4 per cent heme, which is a ferrous complex of protoporphyrin, and 96 per cent

globin. It is taken up from the blood by phagocytic cells which are anchored within the capillaries of the liver, spleen, and bone marrow—reticuloendothelial system, where it is split. Oxidation occurs and the ring opens with the formation of verdohemoglobin. Verdohemoglobin is actually a biliverdin-iron-globin complex. The iron is split off and travels in the globulin fraction of the plasma, leaving the bilirubin globin which remains with the serum albumin. The globin remains attached to the bilirubin until it passes through the liver cells, where the latter is converted into sodium bilirubinate and is excreted into the bile canaliculi with the rest of the bile. Bilirubin globin exhibits a delayed or indirect Van den Bergh reaction and is not excreted in the urine, whereas sodium bilirubinate exhibits a prompt Van den Bergh and is readily excreted in the urine. When the bile reaches the duodenum the bilirubin is reduced by bacteria to mesobilirubinogen and to stercobilirubinogen. These together are known as urobilinogen. The former on exposure to air is oxidized to urobilin 9 alpha, the latter to stercobilin. These two collectively are known as urobilin.

The urobilinogen is either[1] excreted in the feces as urobilinogen, or[2] reabsorbed from the intestine into the blood stream where it is either[a] conducted to the liver and re-excreted in the bile or[b] conducted to the kidneys and excreted in the urine.

Various methods have been used for estimating the amount of bile pigment in the body fluids. The Van den Bergh reaction is probably the best known of these and has formed the basis of several classifications of jaundice. In the older qualitative method of doing the test four types of reaction can occur: (1) immediate direct—this measures the direct reacting bilirubin, that is, the sodium bilirubinate; (2) delayed (30 seconds to 2 hours)—this measures the indirect reacting bilirubin, that is, the bilirubin globin; (3) Biphasic (immediate color gradually deepening)—this measures the direct and indirect bilirubin; (4) Negative—no bilirubin is present.

The newer, quantitative method of doing the Van den Bergh test is a photoelectric method. The first part of the test measures total bilirubin, that is, sodium bilirubinate and bilirubin globin. The second part of the test measures the direct or sodium bilirubinate. In order to get the indirect type, bilirubin globin, one subtracts the latter from the former. This method gives accurate figures and also has the added advantage that the D (direct) over T (total) ratio is instructive, 70 per cent usually being found in the obstructive type of jaundice, 15 per cent in the hemolytic type, and 40 per cent where liver damage occurs with impaired excretion and obstruction.

The delayed or indirect reaction measures the bilirubin which the liver has failed to remove from the blood, that is, bilirubin globin. The immediate or direct reaction measures the bilirubin which has passed through the liver cells into the bile canaliculi and which has subsequently found its way back into the blood because of obstruction of ducts or necrosis of liver cells. This is sodium bilirubinate and in this case the whole bile containing bile acids and cholesterol as well as the bilirubin has been regurgitated into the blood.

With the true direct reaction in the blood it is found that the urine contains bilirubin and may contain bile salts as well. This is because the sodium bilirubinate is unbound and, therefore, can pass through the kidneys.

With the indirect reaction there are no bilirubin or bile acids present in the urine; however, there is an increase in urobilinogen. This is due to the fact that the bilirubin globin is bound to plasma protein and so cannot pass through the kidney filter. The urobilinogen is increased (1) because more bilirubin is excreted to the intestine and so more urobilinogen is formed and subsequently is absorbed back into the blood and (2) because there is subnormal function of the liver and it therefore removes less urobilinogen from the blood to be re-excreted in the bile.

With the direct reaction in the blood the fecal urobilinogen is decreased because the liver has difficulty excreting the bilirubin into the intestine. With the indirect reaction the fecal urobilinogen is increased because there is an increased production of bilirubin and hence an increased formation of urobilinogen in the intestine.

The icterus index is a useful guide in following patients with jaundice; however, it has the disadvantage that it measures the presence of any pigment in the blood, not only bilirubin.

Rich has suggested the following classification of jaundice:

1. *Retention Jaundice.*—This is due to the overproduction of bilirubin combined with subnormal liver function due to various causes. The liver shows cloudy swelling and atrophy but there is no necrosis or blocking of ducts. The blood shows an indirect Van den Bergh reaction. There is an increase of urobilinogen in both the urine and stool.

2. *Regurgitation Jaundice.*—This is due to the rupture of bile canaliculi from various causes. The liver shows necrosis of cells and obstruction of bile ducts. The blood shows a direct Van den Bergh reaction. The urine shows an increase in bilirubin and bile salts but a decrease in urobilinogen. There is a decrease of urobilinogen in the stool.

If one now considers the data presented with regard to the case of M. L. B., it is apparent that this was primarily a regurgitation type of jaundice. Furthermore, all of the possible causes of regurgitation jaundice can be easily ruled out with the exception of infectious hepatitis, acute yellow atrophy, and tumors of the liver. The following brief review of the latter conditions may help to clarify the problem.

Epidemic catarrhal jaundice and nonspirochetal jaundice became known as infectious hepatitis in 1937, when it was realized that the infection is localized in the liver rather that in the duodenum and large bile ducts. The term *homologous serum jaundice* is used to refer to hepatitis artificially acquired from any cause. The clinical picture is the same as in infectious hepatitis; however, the incubation period is longer in serum jaundice, and having one of these does not give immunity to the other. Furthermore, the stools are infective only in infectious hepatitis. It is probable that there are two types of hepatitis virus which are closely related. At the present time homologous

serum jaundice includes cases acquired after the administration of yellow fever vaccine, measles antiserum, mumps, convalescent serum, and transfusions.

The etiologic agent in this disease is a specific virus; however, it has not been grown in the laboratory.

A susceptible person acquires the condition from a patient with the disease, probably by droplets, contaminated food, or water. The possibility of nonicteric patients as potential carriers is being explored.

The onset of the disease may be grippelike in nature or consist chiefly of gastrointestinal symptoms of an abrupt or gradual nature. In children, apathy, listlessness, and drowsiness are very common. Usually the first signs are bile in the urine, followed by yellow sclerae and yellowness of the skin which last about two weeks. If the clinical picture of hepatitis persists for more that three weeks, one should reconsider the diagnosis or think of irreversible changes in the liver which are going on to acute yellow atrophy. In addition, there are frequently anorexia, vomiting, abdominal pain, diarrhea, gray-colored stools, headache, fever, central nervous system symptoms, backache, and edema. On examination one notes the jaundice, the enlarged liver, and occasionally an enlarged spleen.

Laboratory findings usually reveal a white blood count which ranges from 10,000 to 12,000 and falls to 8,000 with a relative lymphocytosis. The liver function tests vary. The Van den Bergh is direct at first, then diphasic as recovery begins, and in the terminal phase of recovery is indirect. The urinary urobilinogen is increased at the onset of the jaundice, then disappears when complete regurgitation of bile occurs, only to reappear again with recovery. The urobilinogen is decreased in the stools.

The prognosis in this condition is good. The mortality is 0.1 per cent to 1 per cent.

Acute yellow atrophy is caused by various toxic agents including the heavy metals, mushroom poisoning, and infections. Clinically the picture is very similar to infectious hepatitis except that the patients' jaundice and symptoms become rapidly worse and they die within a short time.

The tumors of the liver can be divided into two groups, primary and secondary. In the primary type, the benign variety are usually very slow-growing and the malignant equally rapid. The latter may show evidence of local and generalized spread. In the secondary type, neuroblastomas are the commonest, and here one has the signs of the original lesion.

With the above possible diagnoses in mind, we will now go on to a description of what was actually found at post-mortem examination.

SUMMARY OF PATHOLOGY

The body was that of a fairly well-developed but poorly nourished white female infant with dark yellowish discoloration of the skin, sclerae, and mucous membranes. On internal examination all the viscera showed a yellowish discoloration.

There was a moderate, generalized lymphadenopathy and microscopically the lymph nodes were hyperplastic and congested.

Both lungs showed only scattered hemorrhages but microscopically there was evidence of passive congestion and scattered areas of atelectasis.

The spleen was moderately enlarged, weighing 34 Gm. (normal 22). It was purplish-red in color, smooth, and firm in consistency. On cross-section it appeared normal. However, microscopic examination showed evidence of passive congestion.

The intestine was filled with a dark brownish-black material which was probably indicative of hemorrhage; however, the mucosa appeared normal.

The organ which showed the most marked changes and the one which interested us most was the liver. It weighed 344 Gm. (normal 274). On gross examination it was noted to be enlarged, reddish-brown in color, smooth, and firm in consistency, except for two small areas, one in the right lobe and the other in the left lobe of the liver; these were yellow in color and firmer in consistency than the remainder of the liver. On cross section the latter areas were very light brown in color, homogeneous, and fairly well-demarcated from the surrounding parenchyma. The parenchyma was pinkish-brown in color and the lobulations could not be made out distinctly.

The gall bladder and the biliary ducts appeared normal.

On microscopic examination of the red areas, or the so-called normal-looking parts of the liver, it was noted that the liver cells had disappeared completely, but the lobules could still be outlined by proliferating ducts. The sinusoids were present and greatly engorged. The reticulum framework of the lobules was not destroyed and throughout there were scattered numerous, inflammatory cells and macrophages. This was the result of a destructive process, the entire lobules throughout large areas of the liver having been reduced to skeletal frames. Here, where the inflammatory reaction is so evident, is where the name *hepatitis originated*. These changes begin in the central part of the lobule and any fragment of hepatic parenchyma that still remains is found in the peripheral zone. In the area of destruction some of the inflammatory cells have engulfed small granules of yellow pigment (lipofuscin). It is probably a normal pigment of the liver cells which is liberated and rapidly phagocytosed when these cells disintegrate. This serves as an indicator of breakdown of hepatic parenchyma. The rapid cell destruction and removal of the debris is very characteristic of this type of atrophy and distinguishes it from those caused by heavy metals and poisons, where there is evidence of cell death.

In the nodular yellow areas the tissue was in a state of regenerative hyperplasia. The hepatic cells had been formed but the architectural pattern only rarely approached the normal. It began with the presence of binucleated or multinucleated liver cells extending from the remaining portions of hepatic columns into depleted stroma. The marked degree of ischemia of the hyperplastic tissue stood out in contrast to the great engorgement of the tissue in the areas of red atrophy. Beside the regenerative changes in the liver cells there were proliferative changes in the bile ducts, especially in the septal ducts.

During the last war Lucke had the opportunity to study 125 cases of fatal epidemic hepatitis. He was able to show that idiopathic yellow atrophy represents the extreme lesion of epidemic hepatitis and, further, that this yellow atrophy differs anatomically from the yellow atrophy caused by heavy metals and other chemical agents, that of eclampsia, and that of a number of bacterial infections.

The pathologic lesions described in the case of M. L. B. are typical of those seen by Lucke. Furthermore, the clinical picture and laboratory findings which he found in the reviewing of his cases are also very similar. This proves undoubtedly that we were dealing with a case of hepatitis that went on to yellow atrophy.

The next problem was to determine where this child contracted her disease. Homologous serum jaundice was ruled out by the fact that she had not deceived any convalescent sera or transfusions prior to her illness. Hence she must have contracted infectious hepatitis from a carrier, who to this date remains undiscovered.

DR. BIGLER.—Why was the urobilinogen level quoted within normal limits?

DR. PEDVIS.—In this type of jaundice the obstruction is not complete and therefore some sodium bilirubinate can get through to the intestines where it is converted into urobilinogen and therefore appears in the stools. Some of the urobilinogen is reabsorbed and so again a small amount appears in the urine.

DR. BIGLER.—How do you differentiate between infectious hepatitis and acute yellow atrophy?

DR. PEDVIS.—The course in yellow atrophy is much more rapid, all the functions of the liver are depressed to very low levels, and tyrosine is found in the urine.

DR. BIGLER.—Is choline or methianine of value in the treatment of this condition?

DR. PEDVIS.—A recent review in the bulletin of the Johns Hopkins Hospital concludes that these substances are only of questionable value in the treatment of chronic liver disease.

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Case 3. Barbiturate Poisoning

DR. LEININGER.—Chief complaint: headache, staggering gait, coma.

We are presenting the clinical history of a 10-year-old boy who was admitted to Children's Memorial Hospital in a comatose condition and whose illness, according to the history obtained from the parents, apparently began one month ago. The onset and course up to two days before admission was marked by frontal headache without nausea or vomiting. There had been no particular localization of this headache to the right or left side. The headaches had been frequent in occurrence, had been rather severe in character, but had usually been relieved by aspirin and sleep. At no time had the patient complained to his parents of symptoms which could be ascribed to the aura of a migraine attack. Apparently no ataxia had been present or at least observed during the above period. However, two days before admission he was scuffing in bed with his father when he suddenly complained of dizziness and went to

his room. He stated that he had a "funny feeling in his head." At this time he did not complain of nausea or vomiting, but he had no desire to eat. He slept until 5:00 P.M. and then came downstairs where he was observed by his parents to stagger and bump into chairs. They seemed to feel that he had a tendency to veer forward and to the left. He was helped back upstairs and was placed in bed. At this time he complained of diplopia. He slept restlessly through the night and had to get up three times to go to the bathroom. On each occasion it was necessary for his father to assist him because of his staggering gait. The following morning he seemed somewhat improved but his eyes "didn't look right." He seemed to hold his head back and looked out from beneath half-closed eyelids with a vacant stare. His parents described his appearance as that of an individual peering through the near-vision lenses of bifocal glasses. He slept all afternoon. In the evening he cried a lot, complained of a mild headache, was quite restless, and wanted someone constantly near him. He was seen by a local physician in the evening and at that time he was able to perform finger-to-nose tests, and so forth, without any difficulty. Upon the advice of the physician he was sent to bed without specific treatment. About 11 P.M. he fell out of bed and did not seem to recognize his parents. He was quite restless for about one and one-half hours, after which he became comatose and displayed urinary incontinence. Upon the advice of a member of our attending staff, he was admitted to the hospital the following morning.

Physical examination on admission revealed a well-developed, well-nourished, white boy who was lying quitely in bed in coma. His temperature was normal. His pulse was full, regular, and 80 per minute. He was breathing quietly and regularly, approximately 22 times per minute. There was no evidence of Cheyne-Stokes breathing. Hyperpnea was not present. There was no acetone odor or other abnormal odor upon his breath. His blood pressure was 100/65. Examination of the head failed to reveal any evidence of injury. There was no rash or evidence of petechiae. The pupils were small, regular, and equal. Fundoscopic examination revealed some fuzziness of the right disc. No hemorrhage or retinal exudate was observed. The remainder of the physical examination was essentially negative except for the neurologic examination, which revealed a comatose child who responded only mildly to strong stimuli. All reflexes, deep and superficial, were absent. The corneal reflex was present bilaterally. Macewan's sign was negative. The Babinski was believed questionably positive. Kernig and Brudzinski signs were negative. There was no nuchal rigidity. The admitting impression was medulloblastoma of the cerebellum with hemorrhage into the tumor.

A complete blood count was normal. X-rays of the skull revealed normal skull table, sutures, and sella turcica. No abnormal shadows were seen. A lumbar puncture was performed. The fluid was crystal clear and was under mildly increased pressure. Unfortunately, the quantity obtained was insufficient for any analysis of the protein and chloride content; however, the sugar was 53 mg. per cent. The Pandy was negative. There were two cells per cubic millimeter and the culture of the spinal fluid was negative.

Dr. Douglas Buchanan saw this child about 1 P.M. At this time the child had aroused somewhat from his coma. He peered from half-closed eyes and answered questions in a sluggish manner. Dr. Buchanan confirmed the remainder of our neurologic examination except that he believed the optic discs were normal and that the blurring of the right disc was due to moderate astigmatism. He did not believe that the Babinski response was extensor. The deep and superficial reflexes were now present. The only additional significant findings that were observed was the absence of upward movement of both eyes upon voluntary effort and upon Bell's maneuver. In addition, there seemed to be a limitation of outward movement in both eyes. At that time x-rays of the skull had not been taken and the lumbar puncture had not been performed. On the basis of history and physical examination only, Dr. Buchanan felt that the most likely diagnosis was rupture of a congenital aneurysm of the circle of Willis.

During the course of the next four hours the child's condition changed astoundingly. At 5 P.M. he was neither comatose nor stuporous. He responded intelligently and promptly to all questions. There was no evidence of ataxia and the previously observed eye findings were now absent. He seemed somewhat euphoric but his parents observed that this was his normal state.

In summary, this child who was comatose at 9 A.M. had gone through various stages of recovery until at 5 P.M. he appeared entirely normal. He was again seen at this time by Dr. Buchanan, and after viewing the x-rays and seeing the results of the spinal tap, he stated that his earlier diagnosis was incorrect and that diagnosis of the condition would have to be deferred for the time being. He did not feel that the child had a neoplasm. The following morning the child was entirely normal. He had spent a restful night and had eaten a good breakfast. In the afternoon the mother came to the hospital and stated that she had found an empty capsule while cleaning the bathroom at home. She stated that there were in the medicine chest similar capsules which had been prescribed for her some fifteen years ago. Each of these capsules was found to contain three grains of Sodium Amytal. Upon interrogation the patient admitted that he took one capsule on Monday morning, two days before admission, and another capsule on Tuesday night, twelve hours before admission. As soon as these facts were obtained a urine specimen was collected and analyzed for barbiturates. The results of the analysis were negative; however, the fact must be remembered that this urine specimen was necessarily collected forty hours after ingestion of the second capsule.

We feel that this case represents an acute barbiturate poisoning manifested by staggering gait, coma, and neurologic findings which suggested a diagnosis of intracranial pathology.

Progress Note.—Since presentation of this case, this child has been home and has gone to school for one month. During this time he has complained of no headaches and has had no recurrence of symptoms similar to those described above.

DR. BIGLER.—What is Bell's Maneuver?

DR. BUCHANAN.—This is a test of considerable value in children and semicomatose individuals to demonstrate the presence of normal conjugate deviation of the eyes, a reflex which is integrated in the mesencephalon between the superior collieuli. The upper eyelids are gently but firmly held open. The more the patient struggles to close his eyes the more clearly he will demonstrate the presence or absence of conjugate deviation. In the former case, the eyes roll upward.

DR. GIBSON.—What methods are recommended for treating barbiturate poisoning?

DR. BUCHANAN.—In children the ingestion of barbiturates is invariably accidental rather than intentional and, consequently, the total dose is usually less than in the adult attempting suicide. For this reason usually only expectant therapy is needed in children. Almost all cases involving children respond very well in six to twelve hours with nothing more than 5 per cent glucose in distilled water by slow intravenous drip. One milligram of picrotoxin as a single intramuscular injection may rarely be necessary.

DR. GIBSON.—Are there ever any residual changes in barbiturate poisoning?

DR. BUCHANAN.—Clinically, there are none. If the poisoning is fatal, there may be toxic, degenerative changes in the neurones of the cortex.

Case 4. Methemoglobinemia

DR. LEININGER.—Chief complaint: blueness.

We are presenting the case of a 15-day-old female infant who was admitted to this hospital on the tenth day of life. The past history revealed a normal pregnancy and uneventful labor and delivery, following which resuscitation of the infant was immediate. There are no other children in the family. The father and mother are both living and in good health. There is no history of familial diseases. The mother states that she saw the child shortly after birth and that the child appeared to be quite normal. The baby was given the first breast feeding on the third day and nursed for three days at four-hour intervals. Following almost every feeding the mother noted that the child regurgitated or vomited projectilely either part or all of the recently ingested food. On the sixth day the attending doctor took the baby off the breast and started a thickened feeding of Farina, evaporated milk, and water. At this time small doses of phenobarbital were given a short time before each feeding. Apparently the infant responded to this regime for she was sent home on the eight day. The mother was instructed to continue with the thickened feedings and was given a prescription of "phenobarbital, belladonna, and a white chalky mixture." At the time of discharge from the hospital the infant had a normal pink color to the skin.

The parents followed instructions implicitly, giving the infant one-half teaspoonful of the medicine a few minutes before each feeding at four-hour intervals. Apparently the infant had no vomiting at home. The only effect that the parents observed following administration of the medicine was that the child would drop off promptly to sleep following the feedings. Shortly after

the 10 P.M. feeding, and following the fifth dose of the prescribed medicine, the parents observed the child's skin appeared dusky in color. The child did not vomit and did not appear particularly sick. The following morning the parents noted that the skin color was now quite dark, sufficiently so that they were greatly alarmed and brought the child to the hospital.

Physical examination at the time of admission revealed a well-developed, well-nourished, well-hydrated, white female infant 10 days old. She was quite active and was crying loud and vigorously. A very peculiar type of cyanosis of the skin was observed. It was not the typical bluish purple cyanosis of a child suffering from congenital heart disease nor the cyanosis of an infant suffering from atelectasis of the lungs, but rather a dirty, grayish-black tinge to the skin over the whole body but more pronounced around the lips, hands, and fingers. Complete physical examination was otherwise negative. The heart was normal in size, contour, and position, and no murmurs were heard. The lungs were clear to auscultation and percussion. The abdomen was neither distended nor scaphoid. The liver and spleen were not enlarged. The kidneys were not palpable. The stump of the umbilical cord was healing well. The anterior fontanel was not bulging. There were no neurologic findings suggestive of meningitis. The admitting diagnosis was methemoglobinemia, cause undetermined.

A complete blood count was normal. Urinalysis was reported negative. A blood specimen was drawn for examination and found to be almost chocolate brown in color. Quantitative analysis of the blood revealed 2.5 Gm. of methemoglobin and a spectographic study confirmed the presence of methemoglobin.

The pharmacist who had filled the prescription was called and we were informed that the prescription consisted of a tincture of belladonna 5 c.c.; phenobarbital 0.5 Gm., chalky mixture q. s. ad 120 c.c. Because of the normal dosage of phenobarbital and tincture of belladonna which was prescribed in this preparation, we were inclined to rule out the possibility of its having any bearing on the patient's present condition. Upon further interrogating the pharmacist, we learned that the chalky mixture which had been used was a preparation which had been compounded some two or three years ago. For this reason, he was unable to tell us precisely the contents of this mixture. Fortunately, the mother had sufficient foresight to bring the medicine with her to the hospital. We submitted it to the laboratory for analysis, especially requesting examination for bismuth subnitrate and nitrites. Qualitative analysis by means of the HCl-1_2-starch test was strongly positive for nitrites.

Before all of the above laboratory data were available, however, we had proceeded on the assumption that this represented a case of methemoglobinemia. A sterile aqueous solution of 1 per cent methylene blue was prepared and 0.5 c.c. was injected intravenously. Following this procedure, the child was observed for change in skin color. Fifteen minutes following injection of methylene blue there was a questionable improvement in the cyanosis. Twenty minutes after injection there was a definite improvement, but the child was

still quite cyanotic. At the end of a forty-five minute period, the child's skin had returned to the rosy pink color of the newborn infant, except for a slight dusky tinge of the toes, fingers, and lips. Clinically, therefore, we believe that the diagnosis of methemoglobinemia was established before we had obtained substantiating laboratory data.

The following day the child's color had returned entirely to normal and the only problem which remained was an inconstant and mild regurgitation of feedings. Occasionally, there was projectile emesis. However, the child responded well to the usual atropine and phenobarbital therapy and is at the present time retaining all feedings and gaining weight. She is now on a regular evaporated milk formula. The atropine has been discontinued and the elixir of phenobarbital has been reduced to one-half teaspoonful twice a day.

DISCUSSION

The problem of methemoglobinemia arises not infrequently in a pediatric hospital. Fortunately it does not occur as frequently as in the past, probably due primarily to the discontinuance of two therapeutic nitrates in diarrhea mixtures, however, bismuth subcarbonate has supplanted the former drug in view of the fact that nitrates have been demonstrated to be reduced to nitrites in the intestinal tract by the action of the normal bacterial flora; second, the appearance and use of sulfanilamide in the treatment of acute infections was frequently accompanied by some degree of cyanosis attributable to the formation of methemoglobin in the blood. The other common drugs which are known to cause methemoglobinemia are the chlorates and the nitrobenzine compounds, especially the aniline dyes. The last case of methemoglobinemia observed in this hospital occurred in an infant following a very brief contact with aniline dyes used in an identification marker in the diapers of a diaper service company.

The amount of methemoglobin which must be present in the blood stream to cause cyanosis is stated usually to be 3 Gm. per cent. However, this will vary in individual cases, as demonstrated by this infant who had a distinct cyanosis with only 2.5 Gm. per cent methemoglobin. The action of methylene blue in regard to methemoglobinemia is very interesting. For some time now methylene blue has been recognized as an invaluable drug in the treatment of cyanide poisoning. In this condition, the injection of large doses of methylene blue is accomplished in order to create a methemoglobinemia, whereupon the cyanide-ion forms a loose bond with the methemoglobin and is rendered inert, following which the injection of potassium thiosulphate removes the cyanide ion as potassium thiocyanide. In the treatment, therefore, of cyanide poisoning, a methemoglobinemia is produced by large doses of methylene blue. On the other hand, many investigators have demonstrated the acceleration of conversion of methemoglobin back to hemoglobin following the injection of small doses of methylene blue. The usual dose of methylene blue recommended in the treatment of methemoglobinemia is 1.5 mg. per kilogram of body weight. This was the dosage used in the treatment of the patient discussed above.

DR. BIGLER.—Would you again list your causes of methemoglobinemia?

DR. LEININGER.—Sulfanilamide, cyanides, nitrates, nitrites, aniline, chlorates, and nitrobenzenes are the most common causes of methemoglobinemia. Of interest and worth noting are the occasional reports in the literature of methemoglobinemia occurring in infants whose milk formulas have been made with well water containing a high concentration of nitrates. In most of these instances cyanosis was not observed in adults drinking the same well water.

DR. GIBSON.—Is it necessary for any treatment other than altering the methemoglobin?

DR. LEININGER.—No. I think we should mention that prior to the use of methylene blue, transfusions of whole blood were used fairly effectively in treating methemoglobinemia. Oral administration of ascorbic acid also has been used, but results have been equivocal. The rationale of using ascorbic acid is based upon the fact that in vitro studies have shown that glucose, ascorbic acid, and niacin all have the property of transforming methemoglobin into oxyhemoglobin.

DR. GIBSON.—Is there any possibility of recurrence after treating a case of methemoglobinemia?

DR. LEININGER.—Not if the original cause is removed. Nitrates and nitrites, which constitute one of the major causes of methemoglobinemia, are absorbed as nitrites into the blood stream. Normally about 60 to 70 per cent of the absorbed nitrite disappears in the body, probably to be converted into ammonia. The remainder is excreted in the urine as nitrates and nitrites.

Psychologic Aspects of Pediatrics

THE BLIND CHILD

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INDIVIDUALS with vision of less than 20/200 after correction are usually considered blind from the point of view of education. Those with vision of 20/70 to 20/200 in the better eye after correction are called partially sighted. A marked limitation of the field of vision will cause a severe enough handicap to classify the child as blind or partially sighted.

Incidence.—Estimates of the number of blind and partially sighted in the United States vary widely owing to the different definitions which are used and the unreliability of the methods of determining the extent of visual handicap. The estimate given by the White House Conference on Child Health and Protection in 1931[1] for school age children was 15,000 blind (about 0.5 per 1000) and 50,000 partially sighted (over 1.5 per 1000 school population) in this country. This is now regarded as too high. In 1948 in the United States almost 7,000 children were in schools and classes for the blind.

Etiology.—A report prepared by the committee on Statistics of the Blind in 1947[2] gave the principal causes of blindness in school children in the United States as follows:

Infectious diseases	19.8 per cent
Trauma	6.6 per cent
Poisoning	0.2 per cent
Neoplasms	3.7 per cent
General diseases	1.4 per cent
Prenatal origin	58.1 per cent
Etiology not specified	10.3 per cent

Conditions of prenatal origin include congenital cataract, retinitis pigmentosa, atrophy of the optic nerve, and glaucoma.

Blindness resulting from infectious diseases (gonorrhea, meningitis, measles, etc.) has been decreasing. Blindness from accident and injury is to some degree controllable, and measures are being undertaken through accident prevention campaigns to eliminate this factor. Consequently there is a relative increase in the percentage incidence of blindness of prenatal origin. In the future retrolental fibroplasia[3] may become a prominent cause of visual impairment.

MENTAL FUNCTIONING

Intelligence.—Special tests, both individual and group, are available for measuring intelligence in the blind.[4] They may be entirely oral, they may be

From The Children's Medical Service of Bellevue Hospital, the Department of Pediatrics, New York University and the New York Infirmary.

dependent upon touch, or they may be given in Braille if the child is familiar with this method of reading. The reliability of the more recent tests is good.

The average intelligence quotient (I.Q.) of the blind is slightly below that of the seeing when tested on a scale prepared especially for the blind. When only those tests are used which can be given in exactly the same way to both groups, the average for the blind is about 10 points below that for the seeing.[5] The percentage of high I.Q.'s, i.e., I.Q. over 120, is somewhat less than in seeing children. The greatest discrepancy is in the relatively large number of low I.Q.'s. Feeblemindedness is much more common in the blind and borderline categories are larger.[6]

	BLIND (PER CENT)	SEEING (PER CENT)
Genius	0.3	0.5
Very Superior	1	2
Superior	5	9
Average	69	76
Dull	12.5	8
Borderline	7	2
Feebleminded	5	0.3

One reason for this may be found in the conditions which cause blindness. Meningitis and encephalitis, for example, may lead to both loss of vision and mental impairment and the same is true for hydrocephalus and intracranial injury at birth. Whether this factor alone accounts for the frequency of low I. Q.'s among the blind as compared with the seeing is not known. The age at which vision is lost does not seem to affect the intelligence.[7]

Learning Ability.—No difference in learning ability was found when blind and seeing children of equal intelligence were tested.[8]

Memory.—The blind do not differ significantly from the seeing in the ability to memorize except that they are superior in special test situations where the material used is of a type with which they have had considerable practice, such as reciting prose passages.

School Performance.—Blind children begin school, in general, somewhat late and they are therefore older than seeing children in the same grade. The schools for the blind in the United States have about the same standards as the public schools, but it takes blind children longer to cover the same amount of work and they therefore show educational retardation when compared with age norms for the seeing. The ones who start school at a younger age seem to do somewhat better than those who enter later.

Reading.—The use by the blind of special raised characters for reading was introduced in 1829 by Louis Braille who was himself sightless. Only about one out of five blind individuals now read Braille. Most are too old or find it too difficult to learn. The blind child of normal intelligence can be taught to read Braille at the end of the first year of study about as well as the seeing child reads print, but more slowly. His reading ability increases from grade to grade although his progress is in general slower than that of the seeing child. On the average the blind read only a third to a fourth as rapidly as the seeing. The rate in seventh grade is about 60 to 70 words per

minute as compared with 200 to 210 words per minute for seeing children. Given enough time the blind read at grade level but below age level. Standard English Braille, grade two, a system which makes use of contractions, is taught to the older children. This adds another difficulty which the seeing child does not encounter and explains, in part, his age retardation in school. Most tests have shown that Braille reading with both hands is fastest. According to German reports reading is faster with the left than with the right hand in one-handed reading[9] but this has not been found consistently in America. As with seeing children there are poor, average, and good readers.

"Talking books,"[10] first conceived by Thomas Edison, were introduced in the 1930's. They are long-playing (15 to 16 minutes) phonograph discs on which most of what is rewarding in classic and contemporary literature is recorded. The books are read by men and women experienced in stage and radio work. Many plays have been recorded with complete sets of actors reading the parts, and recordings for children have been "illustrated" with sound effects. The discs may be obtained on loan without cost from the Library of Congress or they may be purchased from the American Foundation for the Blind. Talking books for school age children are available through the American Printing House for the Blind in Louisville, Kentucky. The portable reading machines may be obtained from a local agency in each state or they may be bought. Thus far a considerable amount of material has been recorded. This method is more rapid than Braille reading.

Electronic and various other devices are being developed with which it is hoped that the blind may be able to read printed material.

Writing in Braille is done by punching small dots in paper with a stylus. In order to be read, the paper is turned over so that the raised dots may be felt and the writing therefore must be from right to left. Machines called "Braille writers" are available and blind children may also learn to use ordinary typewriters.

Speech.—Blind children begin to talk later than the seeing since they must learn to imitate movements of speech which they have never seen. Moreover, they may have been living in the unstimulating environment of an institution, or the parents may be uninformed as to the special help which blind children need in order to learn to talk. Speech defects are quite common. Once they learn to speak they indulge in it more than seeing children. They ask a great many questions, principally about the objects in their environment. Proper names are used frequently.

Clay modeling gives interesting insight into the conceptions which the blind have about the world. They frequently model things to eat and they make human beings with heads much too large and too full of detail.

In spite of the difficulties in learning, the blind of superior intelligence may attain positions of eminence in the world. A notable example is Helen Keller who lost her sight and hearing through illness at 19 months of age. Despite her handicaps she graduated "cum laude" from Radcliff at 28 years of age. She wrote several books in which her optimistic outlook on life and

the excellent literary style show the efficiency of modern education for the blind. Maria Theresa von Paradis, born in the eighteenth century, was blind and was educated by a blind teacher. She became a prominent musician and toured Europe as a concert artist. John Milton became blind when 43 years old. After this he wrote his greatest work "Paradise Lost," as well as several other poems.

Special Abilities.—The blind pay attention to slight changes in pitch and in pressure, thus recognizing movement, objects in the way, etc. This has been called "the sense of obstacles" and is not fully understood at present. No evidence has been produced to support the theory of a special sensory compensation, that is, the increased sensitivity to sound, touch, taste, or smell, so often attributed to the blind. The blind person is endowed neither with superior memory nor with special ability to recognize people by the voice alone nor to interpret their moods, etc., but he can become more skillful in all these activities by practice. Owing to his visual handicap he must rely more on his other senses and so he cultivates them.

PERSONALITY

Certain personality attributes are commonly found in blind children. They are self-centered and less competent socially than seeing children of the same age. The reason for this is to be found in their difficulty in getting about and meeting people. The home environment is necessarily arranged for their convenience and as a result they may be overindulged and relieved of responsibility. One personality study revealed that they were extremely suggestible, felt inferior, had many fear reactions, but accepted their handicap without bitterness. In another survey, of 105 blind children tested, 101 said they would rather be blind than deaf. Other personality tests corroborating these findings showed that, in general, blind children were unduly sensitive, showed less initiative, and were easily discouraged but were not rigid or remarkably withdrawn. As a group they were more "maladjusted" than the seeing. There seemed to be no more tendency for the blind to show introversion or extroversion than the seeing.

Sommers[11] concluded from her study of the adolescent blind that personal and social adjustment of the blind cannot be adequately measured by tests at present available and that the effect of blindness can be evaluated only in relation to the total social environment of the individual. Emotional maladjustments result more frequently from the attitudes of the parents toward the child and his handicap than from the visual disability itself. The environment in which he lives will certainly influence the child's personality. The stultifying effect of residence in an institution is an important factor influencing the personality of many blind children. Custodial care, with little opportunity for education, is the only kind available in most communities for blind children of low I. Q.

The blind child needs help in developing a personality which will make it possible for him to associate normally with the seeing. Fortunately we are

more kind in our relations to the blind than the deaf. The blind child is obviously handicapped and helpless in getting about under most circumstances. We willingly help him. This in turn allows him to develop a more open personality.

EDUCATION

There are two types of schools for the blind. They may attend Braille classes in the same day schools as normal children and thus take part in regular classroom instruction. They thereby benefit from living at home and maintaining contacts with nonhandicapped individuals. The other type is the residential school. There are over sixty of these in the United States at present, most of which are free. An attempt is made to give the child the same educational opportunities and experiences as sighted children. The disadvantage of this type of school, aside from the fact that the child is away from home, is that he is segregated from seeing children and so lacks preparation for living in a sighted world. Efforts are now being made to teach as quickly as possible the special techniques and materials which are necessary, and then to return the blind children to regular day school. With some provision for Braille, talking books, or a reader, many children seem capable of making this adjustment at the end of grammar school.

At present residential schools for the blind provide education for about 90 per cent and Braille classes for the remaining 10 per cent of blind children attending school. In 1948 Braille classes were conducted in public schools in twenty-five cities in the United States. When educational facilities are available, most parents seem able to cope with the blind child in the home.

OCCUPATION

There has been some disagreement as to whether vocational training should be included in the high school course or given later. It has been suggested that if the education were less verbal and more objective it would be more efficient in preparing the blind for the future. In a follow-up study of 337 blind pupils from the Pennsylvania Institute, Sargent[12] found that over one-half (53.7 per cent) were self-supporting or better, and only 18.1 per cent were completely dependent. The occupations most frequently carried on by men were piano tuning and chair caning, and by women housework and chair caning with weaving and basketry next. Recent experiences have shown that many other jobs requiring manual dexterity and concentrated attention can be handled successfully by the blind.

CARE OF THE BLIND CHILD

Guidance.—The parents of the blind child have a difficult task. They must learn to accept their child and not be frightened or bewildered because of his defect. Special institutes and study groups have been set up in various parts of the United States to help them understand how to meet their problems. There are summer camps for blind children and their mothers in some states, and these have assisted materially in establishing techniques of training.[13]

Seeing children learn, in great part by imitation, the techniques of walking, talking, and feeding themselves, but the blind child is deprived of this advantage. The parents must understand that, with help in learning, the blind child will be able to undertake much that a seeing child can do but at a slightly later age. He must have freedom to move about, to manipulate objects, to play with nonhandicapped children, and to do everything for himself that he is capable of doing. He must have a chance to succeed, he must be praised and reassured, and at the same time he needs to be given responsibility within the limits of his developmental status and his handicap.[14]

The blind child needs more help in learning than the seeing child who is constantly stimulated through vision. The seeing child reaches for attractive objects, he crawls toward playthings, he runs to get a toy. A blind child lacks these stimuli and therefore objects must be brought to him. He learns through sounds, touch, manipulation. He needs playthings which provide varied experiences such as toys of different shapes, sizes, and textures, and toys that make different sounds. In presenting an object to the blind child, its name and something of its structure and use should be told to him. "This is a cup. It is white and hard and shiny. It is made of china. Plates are made of china also. This cup has milk in it but it can hold water or tea. It is to drink from." This simple explanation helps the child to recognize the object again. While the child is young it is best to name any object given to him, so that he will be prepared for its weight and size.

There should be sounds in the environment for these mean much to the blind child.[15] The mother should speak when she enters the room and as she moves from place to place. The child can follow her movements by her voice. Music, musical blocks, and squeak toys are stimulating. For the small baby, toys may be tied to the crib in certain places so that he will know where to find them. He can easily reach wooden beads strung across his crib or a squeaky doll tied to the crib rail. When he gets the toy for himself, it is the first step toward independence.

Extra encouragement and help are needed in walking. Fear is a great deterrent. Creeping is rare in blind children. Walking must be encouraged by interesting sounds. At first the child must be led by the parent, then he can go a short distance from one person to another with only a guiding hand, later with only a guiding voice. A play-pen often helps as he can walk about it holding on. When the baby can walk alone, he must be allowed to investigate his environment. At first objects he would bump into or trip over should be removed, but presently he will know objects in a familiar room and avoid them. Deliberate easy walking should be encouraged rather than running about, since falls are likely to frighten the child badly. The child who walks slowly and pays attention will usually sense objects nearby. He should be taught not to stretch out his hand to protect himself since this is an unpleasant mannerism. Rather he should learn to touch objects with the arms at the side as he passes by, so as to become familiar with them.

The blind child of normal intelligence can learn to feed himself without too much difficulty. At first he should hold the spoon with the mother guiding his hand just as any other child. A little more patience is required. Food should be put on his plate in a certain way, meat at the upper right, potato lower right, etc., so that he will know what to expect. Training for self dressing, undressing, and washing may be started at about the same age as for the seeing child. A little longer is needed in learning but with the proper training the blind child will not be greatly retarded.

The blind child should not be confined to the home. He should ride in buses and trains, he should visit friends, he should go to the zoo and listen to the animals. If his parents will describe their appearance at the same time, telling size, shape, and color, he will know much that the seeing child knows, and he will be able to talk more understandingly with other children. The isolation which is inflicted upon so many blind children is really more of a handicap than the lack of vision. Social intercourse is the best way to make the blind child feel at home with other children.

Some blind children retreat into an imaginary world and avoid facing realities. This is much less likely if life is made interesting. Social contacts are the most important part of helping the child to live realistically. A healthy attitude on the part of the parents and siblings will help relatives and friends to accept the blind child in the same way.

Neatness and orderliness are essential to the blind person. It is obvious that he will get about much better if he knows where every piece of furniture is and that he will find his clothes more easily if they are always in their proper places. Also, as the blind person cannot see himself, he must be especially careful about his clothes and his person. The blind child should be taught tidiness at an early age and this should be emphasized until he himself can appreciate the advantages. The parents and siblings, too, must learn to keep the house in order so that the blind child will feel secure in moving about.

In teaching the blind child it is necessary that verbal instructions be given clearly and concisely. He may miss some detail of the total situation, which is readily apparent to seeing people from a gesture or a facial expression. Consequently, the request is not clear to him and he then appears to be stupid, willful, or disobedient when he is really confused.[14]

Preschool teaching is very similar to teaching the seeing child of the same age, except that more conscious effort is required. Children are not accepted into most kindergarten classes of the schools for the blind before 5 years of age. Some blind children and most partially sighted children are accepted in public kindergartens and go to special classes or schools only after 6 years of age. Typewriting gives the child an easy way of written communication and of expressing his thoughts, but does not help him in reading. In general, when the child is ready to read, usually at about 6 years of age, he must be taught Braille. A matter-of-fact attitude about the necessity of his reading with his hands whereas another child reads with his eyes is usually beneficial in helping the child to accept this technique. He needs encouragement in reading and in

undertaking schoolwork, but if of normal intelligence, he will succeed. If the parent will learn Braille also, he will be able to write to his child and read the child's letters without the help of a third person. This gives the child assurance that his parents are interested in helping him in every way and brings the parents closer to the child.

Blind children should be taught as much as possible by actual experience. Models can be used when objects as such cannot be observed. Verbal description alone should be avoided whenever actual experience can be supplied. The sense of touch is the essential medium for the blind child's acquisition of the basic knowledge of objects.

Standards are set up in most states by the Board of Education for the education of the blind and partially sighted.

Most blind children must be taught techniques of behavior which come more naturally to the seeing child who learns through actual observation. They should walk with the head erect and face the person to whom they are speaking. Certain habitual movements are unpleasant and should be discouraged. One of these, repeated rubbing of the eyes, may begin in infancy and persist into adult life. Shaking and rolling the body, poking at eyes and ears, shaking the hands when excited and, if there is some vision, fanning the fingers in front of the eyes are other undesirable mannerisms known as "blindisms." As soon as these habits appear the parent or teacher should attempt to stop them by gentle reminders, and particularly by keeping the child occupied constructively, as these mannerisms are less frequent when he has something interesting to do. They are by no means an indication of inferior mentality and are given up as the child grows older.

As the blind child matures he, like the seeing child, shows increasing interest in music and literature. Parents can assist their children to enjoy these by making use of the radio, phonograph, and concert hall. Blind children can be taught to play various musical instruments. A considerable amount of music is published in Braille and many Braille books are available for children.

Parents should familiarize themselves with modern concepts of the care and education of the blind.[16] They should not neglect, however, the literature on the normal child since the principles underlying the care of the seeing child relate as well to the blind.

Information regarding all aspects of the care of the blind can be obtained from:

The American Foundation for the Blind, Inc., 15 West 16th Street, New York 11, N. Y.

New York Association for the Blind, 111 East 59th Street, New York 22, N. Y.

Books which may be recommended to parents are:

Guide for Parents of a Preschool Blind Child, Commission for the Blind of the New York State Department of Social Welfare, New York, 1945.

Speer, E. L.: *A Manual for Parents of Pre-School Blind Children,* New York Association for the Blind, New York.

Totman, H. E.: *What Shall We Do With Our Blind Babies?* American Foundation for the Blind, New York, 1938.

Tests which can be used for testing the blind:

Individual Tests.—

Interim Hayes-Binet Tests for the Blind 1942, based on the 1937 L-M Series of Terman and Merrill, Outlook for the Blind **37**: 37, 1943.

Wechsler-Bellevue Adolescent Scale, Verbal and Vocabulary Tests, Psychological Corporation, 522 Fifth Avenue, New York, N. Y.

Personality Tests.—

Adaptation of the Vineland Social Maturity Scale for use with blind children by Maxfield, K. E., and Fjeld, H. A.: Child Development **13**: 1, 1942.

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Comments on Current Literature

THE USE OF GLUTAMIC ACID IN THE TREATMENT OF MONGOLISM

THE use of *l*(+)-glutamic acid in the treatment of patients with defective mental function has been based on experimental studies which indicate that this amino acid is peculiarly important in the metabolism of nerve tissue. According to Weil-Malherbe[1] *l*(+)-glutamic acid is the only amino acid known to be metabolized by slices of brain tissue. By in vitro experiments[2-4] it has been shown that glutamic acid acts as a catalyst in complex enzyme chain reactions which are necessary for the production of electrical nerve impulses. Experimental results with white rats indicated that maze learning was significantly enhanced by the addition of glutamic acid to the diet.

Encouraged by results obtained in the treatment of mentally retarded children *(American Journal of Psychiatry)*,[5] Zimmerman, Burgemeister, and Putnam undertook a special clinical study of the effect of glutamic acid on the mental function of patients with mongolism, and in the March, 1949, issue of the *Archives of Neurology and Psychiatry*[6] they publish a preliminary report. Seven typical mongoloid patients, three girls and four boys, ranging in age at the time of the initial test, from 3 years, 6 months, to 14 years, 1 month, were included in the clinical study. These authors point out that the dosage for each patient must be worked out on an empirical basis determined by careful testing and clinical observation. The particular dose of glutamic acid which stimulates maximum mental function is the optimum for a given patient. In this study of seven patients, the range of daily dosage was as follows: 12 Gm., 18 Gm., 24 Gm., 24 Gm. and 48 Gm. Medication was given orally in three divided doses. No side effects were observed except occasional gastric distress. Each patient received glutamic acid for a period of six months.

Prior to glutamic acid therapy, each child was rated by means of the Stanford-Binet intelligence test and the Merrill-Palmer performance test. When the intelligence test was repeated at the end of the six months' period, all seven of the children with mongolism showed some rise in the intelligence quotient after glutamic acid therapy, the increments ranging from 1 to 20 points. The average mental age was raised from 3 years, 6 months, to 4 years, 2 months, a gain of eight months in the six months' treatment period. The authors state: "Our results suggest that, under the conditions of our experiment glutamic acid definitely facilitates mental functioning in our children with mongolism."

In contrast to the gains made on verbal material, the group with mongolism did not show striking improvement on the nonlanguage, or performance, type of test. Approximately the same increment was maintained on motor tests during treatment as that previously recorded in the absence of treatment. Failure to improve the performance on motor tests might be explained on the basis of pathologic changes in the spinal cord as described by Benda,[7] who showed that the spinal cord of patients with mongolism has a characteristic picture ranging from hypoplasia to true fetalism, with arrested development and pathologic differentiation. This type of pathologic involvement of the cord would explain amply the impaired coordination of muscular activity. Zimmerman, Burgemeister, and Putnam point out that learning depends on

the transmission of sensations from the environment by nerve impulses which are integrated into a state of conscious awareness, and intelligence appears to depend basically upon the degree of conscious awareness. Glutamic acid, by aiding the production of electrical impulses, would increase the degree of conscious awareness, thus facilitating the learning process.

This report, although preliminary in nature, offers valid evidence in favor of the use of glutamic acid in the treatment of patients with mongolism. Since mongolism is one of the more serious and more common forms of mental deficiency, and since there is so little to offer therapeutically, any encouraging note is welcome.

RUSSELL J. BLATTNER.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination held at Baltimore, Md., May 7, 8 and 9, 1949.

Dr. Gunnard John Antell, 310 Coral Way, Coral Gables, Fla.
Dr. Robert Thomas Bandi, 901-4 Central Union Bldg., Wheeling, W. Va.
Dr. George H. Barmeyer, The Western Montana Clinic, Missoula, Mont.
Dr. Leo M. Bashinsky, 2028 Highland Ave., Birmingham 5, Ala.
Dr. Selma Buchbinder, 74 No. Village Ave., Rockville Center, N. Y.
Dr. Edgar L. Clayton, 3 Aldin Lane, Levittown, Hicksville, N. Y.
Dr. John Fielding Crigler, Jr., Harriet Lane Home, Baltimore 5, Md.
Dr. George F. Cunningham, 615 Third St., Brooklyn, N. Y.
Dr. Edward Davens, 2411 North Charles St., Baltimore 18, Md.
Dr. Matthew Debuskey, 2412 Eutaw Place, Baltimore, Md.
Dr. John Henry Dent, Tulane University of Louisiana, New Orleans, La.
Dr. Joseph Dolgin, 33 Central Ave., St. George, Staten Island, N. Y.
Dr. Richard Edward Dormont, Louisiana State University, New Orleans 13, La.
Dr. S. Chester Dunn, 227 W. Kleberg, Kingsville, Texas.
Dr. Anny Elston, 242 East 15th St., New York 3, N. Y.
Dr. Theodore S. Golden, 118 Union Ave., Framingham, Mass.
Dr. Seymour Gruber, 640 Eastern Parkway, Brooklyn 13, N. Y.
Dr. Harriet Griggs Guild, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Janet Baillie Hardy, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Paul Harold Hardy, Jr., Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Horace L. Hodes, Sydenham Hospital, Baltimore, Md.
Dr. Laslo Kajdi, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Maurice J. Keller, 101 Federal St., Salem, Mass.
Dr. Marjorie B. Klugherz, 2100 Avenue J., Brooklyn 10, N. Y.
Dr. Bernard Laski, Hospital for Sick Children, 67 College St., Toronto, Canada.
Dr. Harold I. Lecks, 5701 Ogontz Ave., Philadelphia, Pa.
Dr. Elizabeth Sarah Linson, 214 North Potomac St., Hagerstown, Md.
Dr. James Neill Lysaught, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Milton Markowitz, Johns Hopkins Hospital, Baltimore, Md.
Dr. Lillian Francis McMackin, 71 Blue Hill Parkway, Milton, Mass.
Dr. Jack Metcoff, 300 Longwood Ave., Boston, Mass.
Dr. Thomas Edward Mosher, 525 East 68th St., New York 21, N. Y.
Dr. John Oliver Nestor, 2170 North Glebe Rd., Arlington, Va.
Dr. Thomas Lewis Rider, 959 Washington Ave., Albany, N. Y.
Dr. Martin Rothman, 91 Emerson St., Haverhill, Mass.
Dr. Justin Rubin, 5927 Pine St., Philadelphia 43, Pa.
Dr. Marie Esther Russell, 583 Haddon Ave., Collingswood, N. J.
Dr. Edward A. Sawan, 797½ N. Main St., Akron, Ohio.
Dr. Alexander J. Schaffer, 8 East Eager St., Baltimore 2, Md.
Dr. Francis F. Schwentker, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland 6, Ohio.
Dr. George Roland Spence, 904 Ellsworth Dr., Silver Spring, Md.
Dr. Melchijah Spragins, 102 Alleghany Ave., Towson, Baltimore 4, Md.
Dr. Frank Ashbrook Stewart, 34 Bull St., Newport, R. I.
Dr. James B. Stewart, 12900 Euclid Ave., East Cleveland, Ohio.
Dr. Ethon L. Stone, 143 North Jackson St., Jackson, Mich.
Dr. Helen B. Taussig, Johns Hopkins Hospital, Baltimore 5, Md.
Dr. Grant Taylor, Duke Hospital, Durham, N. C.
Dr. William Joseph Temple, 1 Wallace Ave., Covington, Ky.
Dr. Elizabeth Peabody Trevett, 240 Prince George St., Annapolis, Md.
Dr. Maya Stromberg Unna, 23 W. Calendar Ave., La Grange, Ill.

At the annual meeting of the **American Pediatric Society** at Atlantic City, the following officers were elected for 1949-1950:

President: Dr. Philip C. Jeans, Iowa City.
Vice-President: Dr. Katharine Dodd, Cincinnati.
Secretary-Treasurer: Dr. Henry G. Poncher, Chicago.

The next annual meeting will be held at French Lick, Ind., the last week of April, 1950.

The National Foundation for Infantile Paralysis has announced short courses for physicians in the diagnosis and treatment of poliomyelitis patients as follows:

Training Center	*Scheduled Courses*	*For Detailed Information and for enrollment write to:*
Children's Hospital Boston, Mass.	June 13-17 Aug. 15-19	William T. Green, M.D.
City Hospital Cleveland, Ohio	July 18-23 Aug. 8-13 Aug. 29-Sept. 3	John A. Toomey, M.D. Department of Contagious Diseases
D. T. Watson, School of Physical Therapy Leetsdale, Pa.	1 to 3 weeks, depending on need of each individual. Dates to be specially arranged. Emphasis on when to prescribe the respirator and when the rocking bed, with variations to meet the needs of each patient.	Jessie Wright, M.D. Medical Director
Georgia Warm Springs Foundation Warm Springs, Ga.	3 to 6 months, starting July 5, and October 3.	Robert L. Bennett, M.D. Director of Physical Medicine
Stanford University School of Medicine San Francisco, Calif.	3 days—probably the second week in July.	W. H. Northway, M.D. Assistant Dean
University of Colorado Medical Center Denver, Colo.	May 23-28 Nov. 14-19	Winona C. Campbell, M.D. Director of Poliomyelitis Teaching Program

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The **Seizure Division of the Children's Medical Center of Boston** offers a fellowship of six months for work in epilepsy and electroencephalography. For information, write to William G. Lennox, M.D.

The following officers have been elected by **The Society for Pediatric Research** for 1949-1950:

President: Francis F. Schwentker
Vice-President: Harry H. Gordon
Secretary-Treasurer: Robert Ward

The meeting place for 1950—French Lick, Ind.

Book Reviews

Cardiac Catheterization in Congenital Heart Disease by André Cournand, Janet S. Baldwin, and Aaron Himmelstein. 41 East 57th Street, New York 22, N. Y., 1949, The Commonwealth Fund, 108 pages. Price $4.00.

This book was written to explain the theoretical and practical considerations in cardiac catheterization as applied to congenital heart disease. The book is divided into two parts. Part 1 gives in detail in four chapters the equipment and techniques used for the catheterization procedure; complications are also listed. X-ray plates are shown to illustrate the position of the catheter tip in the various chambers of the heart and great vessels. Blood pressure tracings are shown to illustrate the findings in the various chambers of the heart. The different formulas needed for calculation of systemic and pulmonary blood flow are included.

Part 2 includes seventeen illustrative cases of various types of congenital heart disease. Each case has a brief summary of the history and physical examination together with the pertinent laboratory data. The results of cardiac catheterization are completely listed in a diagrammatic fashion, so that it is very easy to see the various malformations which the authors wish to show.

This should be an extremely useful book for anyone who is interested in cardiac catheterization. It should be particularly helpful to those who are in the process of setting up a laboratory for this type of investigation.

CARSON.

Aesculapius Comes to the Colonies. The Story of the Early Days of Medicine in the Thirteen Original Colonies. Maurice B. Gordon, M.D., Ventnor, N. J., 1949, Ventnor Publishers, Inc., 560 pages. Price $10.00.

This is an exceedingly interesting account of medical men and medical practices in the colonial days of America. Each of the thirteen original colonies is considered in a separate chapter. The development is largely along the line of biographical sketches of the early physicians and the part each played in the early days of medicine in their locality. The book is thoroughly illustrated. It is well-written and the doctor will find it good casual reading for his spare moments and relaxation.

The Uses of Penicillin and Streptomycin. Chester S. Keefer, M.D., Lawrence, Kansas, 1949, University of Kansas Press, 72 pages. Price $2.00.

Three Porter Lectures (Series 15) delivered at the University of Kansas School of Medicine by Dr. Keefer of Boston, an outstanding authority on the use of the antibiotics, compose this book. The first lecture is on Penicillin in Medical and Surgical Practice, the second on Streptomycin in the Treatment of Infections, and the third is entitled Antibacterial Agents From Microbes. In these lectures the author has presented the use of the two antibiotics in a direct and clear way. It is an authoritative presentation of their use and limitations which summarizes present-day knowledge.

The Compleat Pediatrician. W. C. Davison, M.D., ed. 6, Durham, N. C., 1949, Duke University Press. Price $4.75.

Dr. Davison in the sixth edition of "The Compleat Pediatrician" has continued to keep it abreast of current medical knowledge. The reviewer checked it for a number of recent developments and found them all in the new text. It is one of the few books that has steadily improved with each new edition, and over the years has won a much deserved place among the books that are "musts" for the pediatrician. We can only repeat previous reviews in THE JOURNAL that it is "invaluable" and "a veritable mine of information." This opinion, expressed in the early reviews, has been definitely established.

Editor's Column

PEDIATRIC RESIDENCIES

THE annual report on hospital residencies of the Council on Medical Education and Hospitals of the A.M.A.* makes for thoughtful reading. The report shows that as of May 1, 1949, there were 211 hospitals approved for "residency training" in pediatrics with a total of 959 positions for residents and assistant residents available. Ten years ago there were only 105 approved hospitals with 330 positions. Thus in a decade the number of approved hospitals has been doubled and the number of positions increased threefold. Much of this has taken place since 1945, when the approved hospitals numbered 131 and the positions 504. This increase of 60 per cent in the number of hospitals and 90 per cent in the number of positions in the last five years resulted in large part from the demands created by the accelerated medical school teaching during the war and after the war by the large number of returning medical officers entitled to continue their education with government aid. If this number of positions continues to be filled in future years, which we doubt, it would mean about 450 young doctors entering pediatrics as a specialty each year and eligible for certification. This would more than double the present number of pediatricians in a decade when it has taken over three decades to train the present specialists.

We question very much if this will happen, but feel that many of the hospitals will be unable to fill these recently created "approved residencies" in the very near future. Already we have heard of a number seeking applicants. The younger physicians will undoubtedly seek residencies in the hospitals where the best training can be obtained, despite the high stipend now paid by some hospitals in comparison with the low stipend paid by many of the better medical centers for children.

It is interesting to note that at present 17,293 residencies are offered in twenty-six specialties in 1,187 hospitals approved for residency training. According to our calculation, if every medical graduate, after a year of internship, spent the next two years in residency training for a specialty, these graduates would fill about 12,000 of the 17,000 residencies offered. It does not take a prophet but only common sense to realize that the balloon of specialty training, which has been so rapidly inflated in the last few years, will soon undergo a partial collapse, to say the least.

*J. A. M. A., May 14, 1949, page 157.